Oculomotor behaviour in healthy subjects, stroke patients and a case of visual form agnosia.

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Abstract

In my thesis I mainly focus on Milner and Goodale's model (1995, 2006, 2008) of two visual pathways. While the dorsal stream is supposed to be involved in on-line action, i.e. to deal with the immediate and accurate response to a present target, they state that the ventral stream comes to action when previously perceived and memorised visual target characteristics are required for memory-guided action (off-line action).

A lot of evidence for the existence of these separate pathways has come from visual form agnosia patient DF who has repeatedly shown an impaired performance for off-line tasks while she has repeatedly shown an almost flawless performance on on-line tasks (e.g. Goodale et al., 1994a). In DF, this functional dissociation is supposed to be corroborated by her relatively spared dorsal and impaired ventral streams respectively (James et al., 2003).

Likewise patients with hemispatial neglect show a pattern similar to patient DF with off-line reaching impairments such as deficits in anti-pointing and delay tasks and relatively spared on-line actions (Rossit et al., 2009b, 2011). Indeed, hemispatial neglect occurs frequently after lesions to the right inferior parietal lobe (IPL) (e.g. Mort et al., 2003) and Milner and Goodale (1995) speculate that the IPL gets input from ventral stream regions, which would explain the observed deficits in off-line actions. However, due to the heterogeneity of the lesions in patients with hemispatial neglect, an anatomical argument is much more difficult to make.

In this thesis I firstly aimed to examine the oculomotor behaviour of neglect patients and secondly of visual form agnosia patient DF in a series of experiments that tap into either on-line or off-line eye-movement tasks to establish whether Milner and

colleagues' (Milner & Harvey, 2006) action dichotomy can be upheld for the oculomotor domain.

In the first experiment I aimed to find an answer to the question of whether the bilateral anti-saccade impairment (Butler et al., 2009) is the result of a vector inversion deficit (inability to perform off-line actions) or an inhibition problem. To do that I expanded Butler et al.'s study (2009) on pro- and anti-saccade tasks by testing the patients' ability to inhibit saccades in an additional fixation condition. In line with Butler et al.'s (2009) study my neglect patients executed many erroneous pro-saccades in the anti-saccade condition and they also showed neglect typical leftward biases in the pro-saccade condition. Furthermore, the results showed that most of the neglect patients were able to withhold eye movements towards targets. As they did not show a general severe inhibition problem it is very likely that the erroneous pro-saccades in the anti-saccade task were caused by a deficit to perform off-line actions rather than by an inhibition problem.

These findings were further corroborated in experiment 2 in which neglect patients were asked to perform a more complex fixation task with interleaved fixation and pro-saccade trials. Although the patients performed worse than the controls, they were able to withhold most eye-movements during the fixation trials. Thus the occasionally executed erroneous pro-saccades in fixation trials might reflect the greater demands of the complex fixation task rather than a general inhibition problem.

The third experiment examined immediate, stimulus-driven (on-line) and delayed, memory-guided (off-line) saccades. The results showed that all patients were more impaired for the off-line saccades than for on-line action. However this impairment might not be neglect specific as no difference was found between stroke patients with and without neglect.

The fourth experiment focused on the ability to perform oculomotor on-line corrections towards perturbed targets that could suddenly and unpredictably change in location. This task required the on-line adjustment of eye-movements to follow the target. Most of the neglect patients were able to correct their saccades in these perturbed trials and general impairments were often connected to parietal lobe lesions, which might involve the visual dorsal stream.

Experiment 1, 3 and 4 were also carried out on patient DF. She showed no general problems in performance in the pro-saccade (on-line) and fixation condition in experiment 1, yet she was impaired on anti-saccades (off-line). In experiment 3 she was able to execute saccades towards presented lines but was again impaired in the off-line condition (delayed lines). In experiment 4 she showed no problems to perform on-line corrections towards perturbed stimuli.

In summary, on a functional level my results support the distinction between on- and off-line tasks that has been established through the use of pointing and grasping tasks, which I have now extended to the oculomotor domain. The neglect patients, as well as patient DF, were impaired for the tested off-line actions while they showed no general deficits for on-line actions.

Declaration

I declare that this thesis is my own work. All sources have been acknowledged in the text and included in the reference section; all quotations from other authors are marked as such in the text.

Larissa Szymanek

Previously published dissemination

Findings reported in experiment 1 have been presented at the first joint meeting of the Experimental Psychology Society and the Spanish Experimental Psychological Society EPS, Granada, Spain (2010).

Findings reported in experiment 2 have been presented at the European Conference on Visual Perception, Regensburg, Germany (2009) and subsequently published:

> Szymanek L, Butler SH, Rossit S & Harvey M (2009). Response Inhibition in Hemispatial Neglect. Perception 38, 176.

Findings reported in chapter 4.3 have been presented at the European Conference on Visual Perception, Regensburg, Germany (2009) and subsequently published:

> Harvey M, Szymanek L, Butler SH & Rossit S (2009). Memory-guided saccade processing in visual form agnosia. Perception 38, 174.
>
> Rossit S, Szymanek L, Butler SH, Harvey M (2010). Memory-guided saccade processing in visual form agnosia (patient DF). Experimental Brain Research 200, 109–116.

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Chapter 1

GENERAL INTRODUCTION

1.1. Two pathways for visual processing

Vision is probably the most important sense to help us to find our way in the world. It gives us information about our surroundings and helps us to recognise people, objects and events. Furthermore it makes interaction with objects or other people possible and provides information to guide skilled actions like picking up a pen. Indeed, visual perception and visual guidance of action appear to be two distinct functions and the existence of a dichotomy for visual processing with two visual pathways has been repeatedly shown.

In their classic study published in 1982, Ungerleider and Mishkin proposed that a ventral stream, which proceeds from the striate cortex to the inferotemporal region, is crucial for object recognition (what) and a dorsal stream, which runs from the striate cortex to the posterior parietal cortex (PPC), plays a role in the localisation of objects (where) (for a schematic layout please see figure (fig.) 1.1). They reported that in monkeys lesions to inferotemporal areas resulted in the impairment of recognising visual patterns, while PPC lesions induced impairments in spatial tasks. Thus, Ungerleider and Mishkin proposed a theory of two independent streams that are used for visual processing, namely for object perception and spatial perception respectively.

Based on Ungerleider and Mishkin's model, Milner and Goodale (Goodale & Milner, 1992, 2004; Milner & Goodale, 1995, 2006, 2008) developed their theory of two pathways more than 15 years ago. Their model distinguishes between vision for perception and vision for action that operates on different time scales. While the visual ventral stream is supposed to allow object characteristics to be maintained over time and to drive visual perception, the visual dorsal stream is supposed to work in real-time for immediate use in guiding actions.

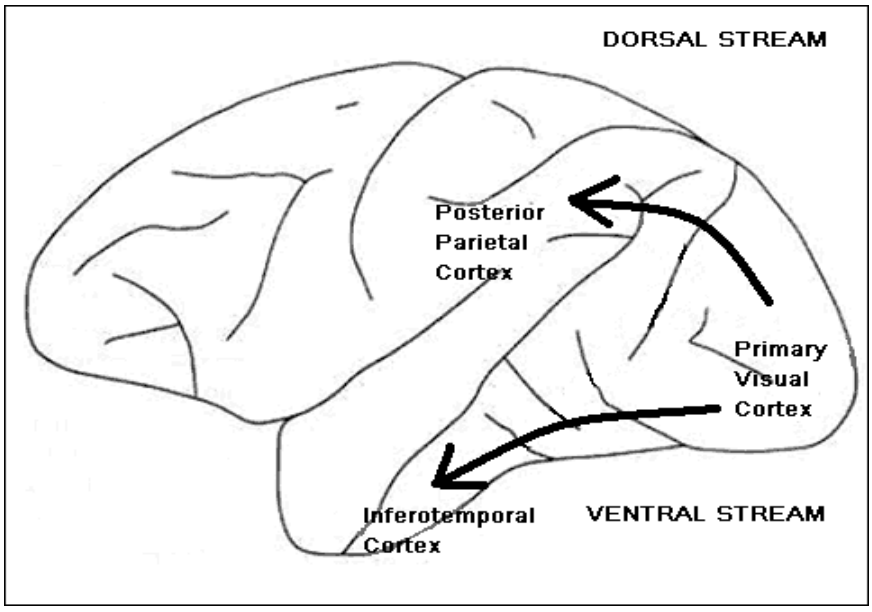


Fig. 1.1: Schematic layout of the two neural pathways for visual processing (e.g. Ungerleider & Mishkin, 1982; Goodale & Milner, 1992; Milner & Goodale, 1995) with the dorsal stream proceeding form the striate cortex to the PPC and the ventral stream proceeding from the striate cortex to the infereotemporal cortex.

Additionally, Westwood and Goodale (2003) proposed in their real-time theory that the dorsal stream information decays quickly, although it generates highly accurate responses when the target is visible. On the other hand, for delayed, memory-guided movements the ventral stream is supposed to generate a response using the stored representation of the previously perceived target. Their experiment on on-line and off-line action provided evidence for the theory. Westwood and Goodale presented targets that were either visible (on-line) or occluded (off-line) in the moment the response was cued. Furthermore, they used a delay of 2,500 ms in some of the on-line and off-line trials before the cue appeared. Alongside the target, a distractor of either the same size as the target (or bigger or smaller) was presented and remained visible all the time. Participants had to grasp the target and results showed that the occlusion had similar effects for immediate and delayed trials resulting in decreased accuracy, while participants performed better in trials in which the target object was visible. The authors concluded that the performance difference between occluded and visual trials is related

to the two different streams. Thus, in trials in which the target is visible at the time the cue is presented and a response is required, the PPC, which is supposed part of the dorsal stream, is involved. Contrary, if the target is not visible when the response is cued the ventral stream takes over and accesses stored representation.

Cohen et al. (2009) investigated the function of the dorsal and ventral visual stream by using Transcranial Magnetic Stimulation (TMS). They applied TMS during immediate and delayed grasping tasks over the anterior intraparietal sulcus (IPS), which is supposed to be part of the dorsal pathway, and the lateral occipital (LO) cortex, which belongs to the ventral pathway. Results revealed that delayed performance was impaired, when TMS was applied over the LO. This is in accordance with Milner and Goodale's model, which proposes that the ventral stream represents a target object long-term and plays a role in memory-guided action. Contrary, TMS over the anterior IPS resulted in an impaired performance in immediate and delayed trials. Thus, Cohen et al. concluded that while the dorsal stream contributes to the online control of grasping an object, both steams are needed to perform a memory-guided action with the dorsal stream controlling the actual grasping and the ventral stream controlling the grip aperture that is based on the remembered target.

However, unlike Westwood and Goodale (2003) who propose an immediate change from the dorsal to the ventral stream processing once the target is occluded, Himmelbach and Karnath (2005) found evidence for a more gradual change between the streams. They tested two patients with optic ataxia (see 1.1.1. below for definition of the disorder) who suffered from lesions to the visual dorsal stream, on a pointing task with four different delays (0, 2, 5 and 10s). According to the real-time theory one would expect the patients to improve their actions once they had to perform a memory-guided action in trials with delays of 2, 5 and 10s. Yet there was no sudden improvement but results indicated a more gradual improvement with an increasing delay.

In addition, Rogers, Smith and Schenk (2009) found evidence for immediate and delayed action using similar visuomotor processes. They investigated immediate and delayed pointing performances before and after prism adaptation. The results showed that immediate pointing during prism adaptation not only influenced post-adaptation immediate pointing but that it also had an after-effect on delayed pointing. Likewise, delayed pointing during prism adaptation influenced post-adaptation immediate and delayed performances, thus leading to the assumption that on-line and delayed pointing underlie the same processes in visuomotor tasks.

So although there is some evidence questioning the separation of immediate and delayed actions in terms of their relative reliance on dorsal and ventral stream processing, Milner and Goodale nevertheless argue that there are different types of actions and that these in turn depend on different cortical networks (Milner & Goodale, 2006; Goodale, Westwood, & Milner, 2004). For the immediate guidance of action spatial information is coded in egocentric coordinates and depends on the visuomotor networks of the visual dorsal stream. On the other hand, when the action is not directly target-driven and thus requires relational metrics and scene-based coordinates (referred to here as off-line processing in a wider sense than that used by Westwood and Goodale, 2003; see Rossit et al., 2011) the ventral stream is involved.

I will first review evidence for this differential processing from findings in patients with visual form agnosia and optic ataxia where clear functional differences emerge between on-line (dorsal) and off-line (ventral) functions. Moreover, more recent data has shown that the visual dorsal stream may also be spared in patients with hemispatial neglect as they can carry out on-line tasks deemed to rely on dorsal stream function, and I will review these. The aim of my thesis is then to assess whether these different types of actions can also be teased apart in the oculomotor domain when

testing patients suffering from hemispatial neglect and visual form agnosia and I will review the very limited studies that have so far been done investigating this.

1.1.1. Evidence for the visual pathways from visual form agnosia and optic ataxia

Clear evidence for the existence of two separate pathways for visual processing comes from studies on visual form agnosia, in particular patient DF, and optic ataxia. DF, who suffered from carbon monoxide poisoning in 1988, shows a lesion to the ventral stream while her dorsal stream remains intact (James et al., 2003). On the other hand, lesions to the PPC, an area in which the dorsal stream is supposed to terminate, often cause reaching impairments in humans and monkeys which is referred to as optic ataxia (e.g. Milner & Goodale, 1995; Karnath & Perenin, 2005).

Goodale and his colleagues (1994a) tested visual form agnosia patient DF and optic ataxia patient RV with an object discrimination task and a grasping task. The results showed an interesting dissociation between the two patients. In the discrimination task, DF was unable to identify if two simultaneously presented objects were the same or different. Conversely RV showed only little impairment on this task. In the grasping task, the participants had to pick up random shaped objects with thumb and index finger. Paradoxically RV had great difficulties to grasp the objects correctly in this task, although she was previously able to visually discriminate the objects. However, patient DF was able to place her fingers on appropriate opposition points to pick up the objects, although she performed very poorly in the previous visual discrimination task. Goodale and colleagues concluded that these results provide evidence for distinct processes for the perception of objects and the control of interaction with these objects.

This double dissociation has been observed repeatedly in a number of studies that included patient DF and optic ataxia patients. It has been found that DF's visuomotor system is able to adjust her actions to the orientation and size of a target object, but that her performance appears to be impaired when no actual interaction with the object is required (e.g. Milner, 1991; Goodale et al., 1994a; Carey, Harvey & Milner, 1996).

DF showed for example that she was able to coordinate correctly motor behaviour towards a visually presented object and performed very well when she had to adjust her hand in relation to slots of different orientations. However, when she was asked to make a verbal or manual judgement without actually reaching for the target she was impaired (Milner, 1991).

To examine DF's ventral and dorsal stream activation directly, James et al. (2003) used functional Magnetic Resonance Imaging (fMRI) while testing her with a perceptual object recognition task and an object-directed grasping task. Unlike healthy control participants, who showed greater LO activation for line drawings of objects compared to scrambled line drawings, DF did not show any activation difference between the stimuli. These results are in line with her lesion that involves area LO in the ventral steam and DF's poor performance when she has to identify an object. On the other hand, DF showed normal dorsal stream activation in the anterior IPS during a grasping task, which matches her ability to correctly interact with objects directly.

Beside her impairment in recognising objects and in agreement with Milner and Goodale's theory that the ventral stream stores object characteristics over time, DF showed poor performance when she had to execute pantomimed pointing tasks (Milner, Dijkerman and Carey, 1999; Carey et al. 2006). For example Carey and his colleagues used targets (tokens) that were arranged on an array. In a direct pointing condition, participants had to point to a specified target or sequence of

targets while in the pantomime pointing condition, they were required to point, on a blank sheet that was placed next to the actual array, to the identical location as if the specified token was there. DF performed very well in the direct condition but showed a clear impairment with a pointing accuracy in the pantomime condition.

Likewise, she was impaired in carrying out memory-guided saccades towards previously presented lines after a 2,000 ms delay (Rossit et al., 2010; see also chapter 4.3). Here, DF also showed greater inaccuracy in the memory-guided saccade task compared to an immediate condition in which she was required to saccade towards a target line that was present.

The opposite response patterns were found in optic ataxia patient IG, who showed an increased accuracy of her grip aperture in proportion to the object size when she had to delay her grasping movement compared to immediate grasping trials (Milner et al., 2001). To assess further whether the patient used her memorised information rather than the on-line information of the actual presented object in the delayed task, Milner and colleagues conducted another delayed pointing task. In this task an object was exposed and after a delay of five seconds during which the target was occluded, the same target re-appeared or a target of different size was presented, thus making the memorised and the actual target information incongruent. As soon as the target re-appeared after the delay, the patient had to grasp it. The results gave evidence that IG used the memorised information as she performed poorly in the incongruent tasks, while she had no problem to immediately adjust her grip aperture to the object, when it had the same size as before the occlusion period. Similar results were found for a pointing task in which optic ataxia patients AT and IG showed a better accuracy for delayed pointing movements towards a target compared to immediate pointing movements (Milner et al., 2003; see also Milner et al. 1999). Again the effect of incongruent and congruent trials was tested by presenting a target at one of two possible locations and

after a delay of five seconds during which the target was occluded, it re-appeared at the second location in 25% of the trials or in 75% at the same location. As for the pointing task, both optic ataxia patients performed poorly in the incongruent tasks, giving evidence that they used the memorised rather than the on-line information.

As explained above, optic ataxia patients show an impairment in on-line actions. Evidence for this was also found when they had to perform automatic movement corrections towards a target that suddenly changed position. While healthy participants were able to automatically change their pointing direction in one smooth movement in trials with a perturbed target, the corrections of optic ataxia patients with lesions to the PPC appeared to be much slower and deliberate (Pisella et al., 2000; Grea et al., 2002; Blangero et al., 2008). Moreover, Grea et al. (2002) also found that optic ataxia patients needed a greater number of movements to follow the perturbed target, with the first pointing movement terminating at the location where the target had previously been (before correcting the movement towards the new location).

These studies give an overview of the different abilities of visual form agnosia patient DF and optic ataxia patients that support a double dissociation. These differences also provide evidence for the existence of two visual streams: the dorsal stream for visual control of on-line action, which is usually affected in optic ataxia and mostly spared in DF, and the ventral stream for visual perception and long term representation of object characteristics (off-line processing), which is affected in patient DF while it is spared in optic ataxia. I will now describe the disorder of hemispatial neglect and the evidence that has been accumulated so far, indicating that actions that rely on visual dorsal stream function are relatively spared in these patients. On the other hand, when the action is not directly target-driven and thus requires relational metrics and scene-based coordinates (off-line actions) clear deficits can be found.

1.1.2. Hemispatial neglect and the visual pathways

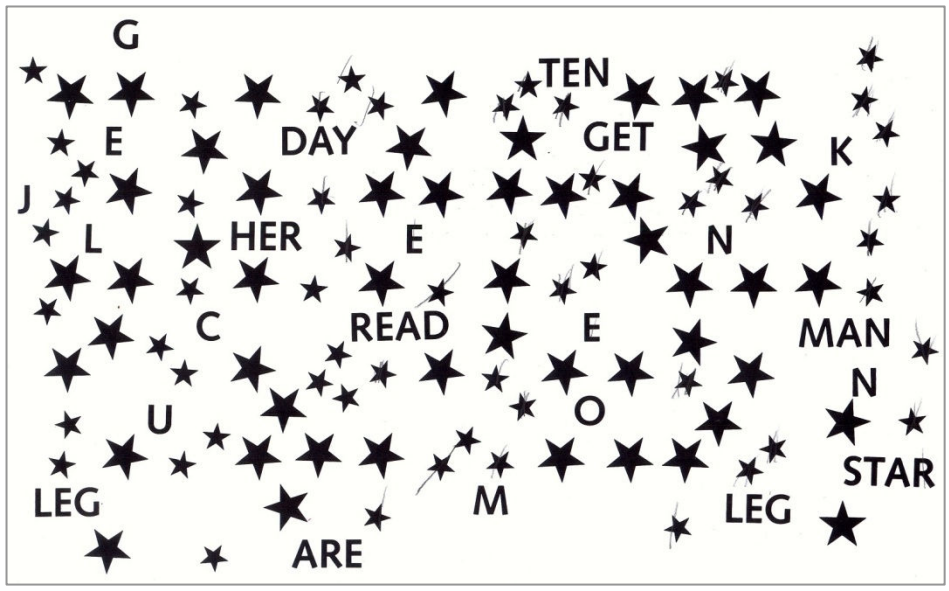
Symptoms

Hemispatial neglect is generally defined as the inability to direct attention to the contralesional, usually the left, side of space (Heilman, Valenstein & Watson, 1985). While in everyday life neglect patients miss objects on the left side, bump into things on the left side or even forget to shave the left side of their face, they also often fail to respond to left stimuli in experimental settings (e.g. Girotti et al., 1983; Niemeier & Karnath, 2003) and during the free exploration of natural scenes (Müri et al., 2009). For the left hemifield, Girotti et al. (1983) reported a saccadic absence of 25%. However, for the right, ipsilesional side, the neglect patients in their study never missed a target. Furthermore, neither the healthy controls nor patients without neglect failed to respond to any target.

Neglect patients also show an impairment when they are required to bisect a horizontal line. This task often results in rightward errors with the neglect patient displacing the midpoint to the right side (e.g. Nichelli, Rinaldi & Cubelli, 1989; Halligan, Manning & Marshall, 1990). Figure 1.2 shows examples of the typical performance of a neglect patient in two subtest of the Behavioural Inattention Test (BIT, Wilson, Cockburn & Halligan, 1987) with omissions on the left side of the array in a detection task and midpoint displacements to the right side in a line bisection task.

Moreover, Milner and Harvey (1995) showed that neglect patients underestimated the horizontal extent or area of stimuli presented on the left side, while the vertical extent was perceived correctly when making judgements on target pairs of horizontal rectangles, vertical rectangles or nonsense shapes.

(a)



(b)

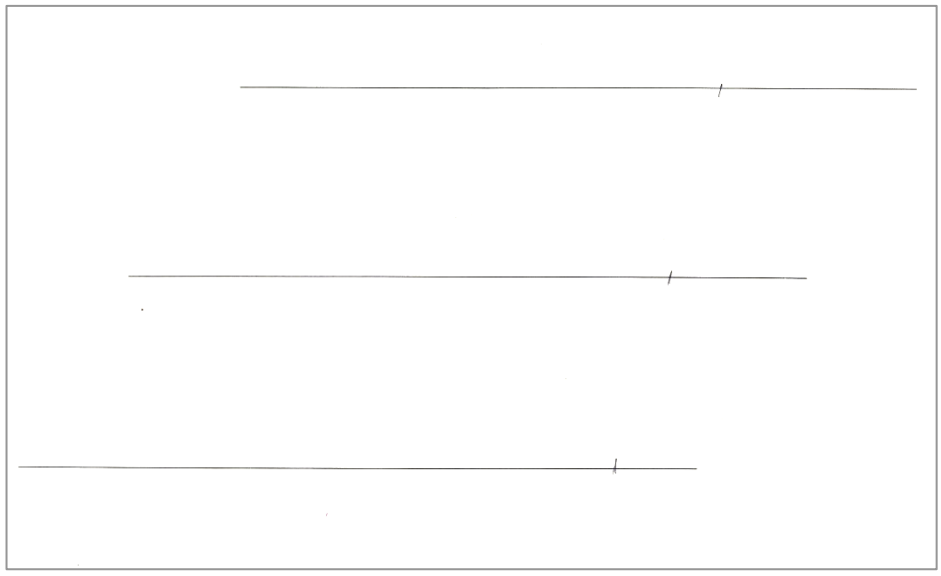


Fig. 1.2: BIT subtests “star cancelling” (a) and “line bisection” (b); neglect patient PI (see also chapter 2 and 3).

While most studies report an impairment for directing attention to the left side, other studies have found evidence that neglect patients are able to respond to targets on the left side (e.g. Harvey et al., 2002; Butler et al., 2009). For example Harvey et al. (2002) revealed that neglect patients saccaded into the neglected field when the target was presented alone and similarly Butler et al. (2009) reported (despite reduced saccade accuracy with the eye movements falling too short) that the neglect patients responded

to single left targets during pro-saccade trials. Likewise, Niemeier and Karnath (2003) found smaller amplitudes for leftward saccades only in stimulus-driven trials, in which the participant had to saccade towards a particular target, while in the voluntary condition, in which an array had to be searched for targets, no saccade amplitude asymmetries were found. However, increased reaction times as well as more and shorter saccades have been reported in the cases in which neglect patients responded to left stimuli (Girotti et al., 1983; Harvey et al., 2002; Niemeier & Karnath, 2003).

Beside impairments for left targets, Walker and Findlay (1996) reported that neglect patients have difficulties in disengaging from a stimulus (see also Posner et al., 1984). Indeed neglect patients show a tendency to re-fixate targets, for example during cancellation tasks like the BIT subtests "star cancelling" (see fig. 1.2. (a)), apparently unable to disengage from them, while other targets remain ignored. A connection between re-fixation behaviour and parietal lesions was found by Husain et al. (2001) and Na et al. (1999) found lesions to the frontal lobe to play a role in motor perseveration, i.e. that during cancellation tasks the same target is marked repeatedly. Moreover, Rastelli et al. (2008) found evidence that the disengagement deficit is not space based but occurs mostly when neglect patients have to direct their attention away from an object on the ipsilesional side.

Lesion Location

Neglect occurs more frequently after right than left hemisphere lesions (Stone et al., 1992). It is often connected to damage to the parietal cortex (Heilman et al., 1993; Halligan et al., 2003) and in particular the inferior parietal lobe (IPL) (Vallar & Perani, 1986; Mort et al., 2003). Furthermore, the superior temporal gyrus (STG) has been identified as a critical area for neglect (Karnath, Ferber & Himmelbach, 2001; Karnath et al., 2004) and various studies have found evidence for the frontal lobe being involved

in neglect (e.g. Welch & Stuteville, 1958; Heilman & Valenstein, 1972; Damasio, Damasio & Chang Chui, 1980; Husain & Kennard, 1996; Husain et al., 1997). Moreover, Watson et al. (1973) found neglect after unilateral damage to the anterior cingulate gyrus (ACC) and lesions to subcortical structures are frequently implicated in hemispatial neglect (e.g. Watson & Heilman, 1979; Damasio, Damasio & Chang Chui, 1980; Graveleau, Viader & Cambier, 1986). Like Watson and Heilman (1979), Graveleau, Viader and Cambier (1986) reported multimodal neglect after thalamic haemorrhage. They describe a 71 year old man after right thalamic haemorrhage who showed left neglect in various tests like target cancellation, picture description and word and sentence reading. He also did not use his left limbs spontaneously. Furthermore, Damasio, Damasio and Chang Chui (1980) report two subcortical neglect cases after damage to the basal ganglia.

Coming back to the dorsal and ventral stream model of visual processing, Milner and Goodale (2006) claim that the dorsal stream remains relatively spared in hemispatial neglect. As can be seen from the studies reviewed above this argument is very difficult to make in terms of anatomy as a whole range of different lesion sites are implicated in the syndrome. Yet in terms of function it has been shown that neglect patients are able to perform on-line actions, i.e. respond towards targets in the here and now like pointing towards and grasping single targets:

Spared reaching and grasping

Karnath, Dick, and Konczak (1997) who tested acute neglect patients and right hemisphere damaged patients without neglect on a simple pointing task, found no evidence of an impairment in the reach trajectory. In fact, neither patient group varied from the healthy controls in terms of either reach deviation or final accuracy. Additionally, although movement times were longer in the two patient groups compared

to the healthy control group, the velocity profiles of the neglect patients to leftward targets did not differ from those to targets in right hemispace, giving no indication for a direction specific deficit in the control of hand velocity (Konczak & Karnath, 1998; see also Konczak et al., 1999, for similar results). A similar sparing was reported by Chieffi and colleagues (1993) in an earlier experiment in which a recovered neglect patient showed normal reaching and handgrip movements towards single objects. In a similar vein, Pritchard and colleagues (1997; Milner, Harvey & Pritchard, 1998) described a neglect patient who was able to calibrate her finger-thumb grip aperture accurately when reaching to grasp different sized cylinders, with no asymmetry in grip size between target locations on the two sides of visual space. Only when asked to indicate manually the size of the cylinders, did she consistently underestimate them when they were located on her left (as compared with her right) side.

Later studies with groups of neglect patients replicated this symmetrical behaviour for grasping in open and closed loop conditions, i.e. with full vision of arm, hand and target during the response, and with shutter glasses preventing the vision as soon as the pointing movement started (Harvey et al., 2001a), including reaches towards objects of different sizes (McIntosh et al., 2001). Finally, using a pointing task, this time comparing acute as well as recovered neglect patients and right hemisphere damaged patients without neglect, Himmelbach and Karnath (2003) again failed to find any impairments in the neglect groups in either final accuracy or hand trajectory (even when applying all of the different measures of hand path curvature used in previous studies).

Likewise, Rossit et al. (2009c) found that neglect patients showed no overall impairment for the planning and executing of pointing movements, when they had to point either directly towards or halfway between two targets (with and without visual feedback during the movement). Instead they revealed no-neglect specific deficits of

longer latencies for right hemispheric patients with and without neglect for pointing movements towards left targets in trials with visual feedback.

So, as pointed out by Himmelbach and Karnath (2003), it seems that even patients with severe spatial neglect in the acute stage of their stroke, can reach accurately to a target (with or without actual feedback about hand position), and they can do so in both left and right hemispace.

Moreover, in contrast to the optic ataxia patients described earlier, neglect patients can make on-line corrections when a target object is shifted unexpectedly, even when the target shift occurs in a leftward direction (Milner & Harvey, 2006). Farnè et al. (2003) required seven right brain damaged patients (four with neglect) to grasp one of five possible objects spaced 10 degrees apart (whichever was illuminated). On perturbed trials, the target shifted from the central location to one of the other positions (a shift of 10 or 20 degrees). The authors found that on these trials the patients' movement times were longer to make a leftward adjustment than to make a rightward one, a difference not present in the controls. However the illustrative plots of individual trials show that even the healthy controls made very late adjustments on perturbed trials, reaching towards the initial (central) target and then making partial withdrawal movements of the hand while redirecting their reaches. The reason for these late corrections even in the control subjects may have been partly that the target was shifted by a substantial distance (10 or 20 degrees), coupled with the fact that the initial target did not disappear, but simply dimmed, necessitating a choice between an old and a new target. In any event, normal behaviour in this task contrasts with that of the controls in the previously mentioned studies (Pisella et al., 2000; Gréa et al., 2002). In those tasks the controls corrected their reach trajectories early, making seamless movements to the new location, even being drawn irresistibly to it against their own wishes and contrary to the experimenter's instructions (Pisella et al., 2000, Milner & Harvey, 2006).

McIntosh and colleagues have since studied target perturbation in seven right-brain-damaged patients with and eight patients without visuospatial neglect as well as eight healthy controls (McIntosh, et al, 2010). Participants reached with the right index finger for a central target which remained static (70% of trials) or jumped at movement onset by 5 degrees to the left (15% of trials) or right (15% of trials). In separate blocks, the instruction was either to follow the target (GO) or to interrupt the movement in response to the target jump (STOP). Although the analysis of correction time for successfully adjusted movements (all participants corrected the movements in the 'target jump' condition) revealed differentially longer durations to the left compared to the right targets for the neglect group, neglect patients did make corrections to leftward target jumps, even in the STOP condition. The occurrence of such uninstructed corrections suggests that the 'automatic pilot' system is functional in neglect, but trajectory corrections towards the left jumps emerge more slowly than those to the right. In this context it is also worth noting that even in the study by Farnè et al. (2003) patients were not functionally defective in that they still correctly grasped and lifted the perturbed leftward target objects, a behaviour in stark contrast to those of the optic ataxic patients described earlier, who typically completed their movements to the initial location of the target (Milner & Harvey, 2006).

The above reported studies provide evidence that the ability to perform goal-directed, on-line responses, including on-line updating, seems to be spared in most neglect patients and are in agreement with Milner and Goodale's (2006) claim that the dorsal stream remains relatively intact in neglect patients. Milner and Harvey (2006) argue further that neglect should affect action indirectly only; for example where a choice of actions has to be made or when the action is not directly target-driven and thus requires relational metrics and scene-based coordinates, as it is the case in delayed and mirrored (anti-pointing) reaches. The evidence for this is reviewed below.

Impaired reaching and grasping.

A hint that neglect patients may be impaired for delayed actions is given in a report by Darling, Rizzo, and Butler (2001), in which a number of patients with focal brain damage were tested using a delayed pointing task. They found that all of their patients with damage to the inferior parietal lobule (an area frequently damaged in hemispatial neglect) were impaired on this task. This is consistent with the idea that inferior parts of the parietal lobe may play an important role in visuospatial working memory and it has in fact been reported that many neglect patients show a deficit in tasks that tap this ability (Pisella et al., 2004; Malhotra et al., 2005). Yet importantly, visual information first has to be coded as a perceptual representation in order to allow for the possibility of later flexible access to that information through working memory. It is possible that neglect patients will find this encoding difficult, particularly for leftwardly presented targets. In fact when Rossit and colleagues (Rossit et al., 2009b) tested the ability of nine neglect patients (and ten healthy and ten right hemisphere no neglect control groups) to perform reaches towards immediate and delayed targets, placed in left, central and right locations, neglect patients showed no accuracy impairments when asked to perform the immediate action. In contrast, when pointing towards remembered leftward locations, they markedly overshot the targets or failed to initiate a reach altogether. It is thus likely that the neglect-specific deficit in the delay condition was a failure to code the left target location (presumably in allocentric coordinates) for the delayed reach. This argument was supported further by the finding that poor performance for the left targets in the delay task was not correlated with working memory performance, making it unlikely that the deficit was a failure to hold the target in memory *per se* (Rossit et al, 2009b).

In another task, Rossit et al. (2011) tested pro-pointing (pointing towards a target) and anti-pointing (pointing away from a target towards the opposite, mirror

location) in patients with right hemisphere lesions with and without neglect and healthy controls. As predicted, the results revealed no impairment for both patient groups when the participants performed goal-directed responses in the pro-pointing condition. Yet in line with Milner and Goodale's predicitions (2006), neglect patients were significantly impaired in the accuracy of their anti-pointing movements when compared to right hemisphere damaged patients without neglect and healthy controls.

1.2. Rationale for and purpose of the experiments

A lot of evidence for the existence of separate dorsal and ventral visual pathways has come from visual form agnosia patient DF. Her impaired performance for off-line tasks such as pantomimed pointing (e.g. Carey et al., 2006) may be due to her ventral stream lesions in the LO areas (James et al., 2003). Conversely she has repeatedly shown an almost flawless performance when she interacts with the target during on-line tasks like the grasping of objects (e.g. Goodale et al., 1994a). Such on-line actions are supposed to be processed by the dorsal stream which is mostly spared in DF (James et al., 2003).

The findings reviewed above demonstrate that patients with hemispatial neglect show a pattern similar to patient DF with off-line reaching impairments such as deficits in anti-pointing and delay tasks and relatively spared on-line actions (Rossit et al., 2009b, 2011). In DF, this functional dissociation is corroborated by her relatively spared dorsal and impaired ventral streams respectively. Due to the heterogeneity of the lesions in patients with hemispatial neglect, an anatomical argument is much more difficult to make and for the rest of the thesis, in which I hope to demonstrate that the on- and off-line dissociation can also be demonstrated in the oculomotor domain, I will argue more in terms of a functional rather than an anatomical dissociation.

Nonetheless, I outlined earlier that hemispatial neglect occurs frequently after lesions to the right IPL (e.g. Mort et al., 2003), the STG (e.g. Karnath, Ferber & Himmelbach, 2001) and the frontal lobe (e.g. Husain & Kennard, 1996). Singh-Curry and Husain (2009) state that the IPL does not fit into the dorsal-ventral dichotomy of Milner and Goodale's (1995) theory and in fact seems not to be considered in their model. Yet this stance is incorrect as Milner and Goodale (1995) speculate that the IPL gets input from ventral stream regions which would explain the observed deficits in off-line actions described above. Moreover lesion analyses done in the two studies by Rossit and colleagues revealed, for the first time, a connection between lesions to occipito-temporal areas and impaired accuracy for delayed leftward targets (Rossit et al., 2009a). Secondly, for impaired anti-pointing, Rossit et al. (2011) found connecting areas in the middle and superior temporal gyrus and the parahippocampal gyrus to be implicated. Although these areas are not part of the visual ventral stream directly, like the IPS they may well receive input and interact with the ventral stream and as such drive the observed impairments.

1.2.1 Aim of thesis and brief overview of experiments

The aim of this thesis is to examine the oculomotor behaviour of firstly neglect patients and secondly the visual form agnosia patient DF in a series of experiments that tap into either on-line or off-line eye-movement tasks to establish whether Milner and colleagues' (Milner & Harvey, 2006) action dichotomy can be upheld for the oculomotor domain.

In the first experiment (chapter 2) I expand on Butler et al.'s study (2009) on pro- and anti-saccades. They reported previously, that neglect patients produce many incorrect pro-saccades during an anti-saccade task. I aim to answer if neglect patients are unable to perform off-line actions such as looking in the opposite direction from a

target (similarly to their inability to anti-point) or if instead, they are unable to inhibit eye-movements towards a target. I will investigate this by testing the patients' ability to inhibit saccades in an additional fixation condition (2.2) as well as in a more complex fixation task (2.3). If the reason for the errors in the anti-saccade trials lies in the inability to inhibit eye-movements, I would expect errors also in fixation trials where no eye-movement is required. If, on the other hand, patients can withhold saccades in fixation trials this may suggest an off-line remapping failure as the underlining impairment.

I will also test on-line and off-line actions in an immediate and delayed saccadic task, in analogy to the delayed reaching tasks described above (chapter 3.2 and 4.3). Here I expect DF and neglect patients, in line with previous results (e.g. Rossit et al., 2009b), to be unimpaired in the immediate saccades (on-line action), while I predict a deficit in the delayed saccades (off-line task).

Finally I will test the ability to perform oculomotor on-line corrections towards perturbed targets in both neglect patients and DF (chapter 3.3 and 4.4). I have already described that, for reaching, automatic on-line corrections are relatively spared in neglect patients (McIntosh et al, 2010) and I expect neglect patients as well as patient DF to be able to perform oculomotor on-line corrections in perturbed trials.

There has been a lot of evidence from studies into visual form agnosia, optic ataxia and more recently hemispatial neglect supporting the argument that different types of actions depend on different cortical networks and that functional dissociations for on versus off-line actions can be demonstrated. So far virtually no work has addressed the possibility that these functional differences may also be upheld in the oculomotor domain and my thesis is aimed at establishing whether this is the case.

Chapter 2

VOLUNTARY EYE-MOVEMENTS AND INHIBITION IN NEGLECT

2.1. Introduction

The anti-saccades task (Hallett, 1978) is often used to assess voluntary control over stimulus input. In this task the participant has to fixate a central point on a screen and when a peripheral target appears, is required to look away from the target to a mirror location diametrically opposite of the target. Compared to pro-saccades, anti-saccades require additional processes to carry out a correct performance as the participants are required to saccade away from an abrupt onset target. In order to perform this task they have to inhibit the stimulus-driven orienting response to the target, and instead generate a voluntary orienting response in the opposite direction (Hallet, 1978; Connolly et al., 2000).

It has been shown that an anti-saccade task generally causes more errors compared to pro-saccade tasks, with participants making false pro-saccades towards the target instead of looking away, although 50% ±25% of false pro-saccades are not even recognised by the participant (Mokler & Fischer, 1999). A study with 2,006 healthy male participants reported a mean percentage of erroneous pro-saccades of 22% (Smyrnis et al., 2002).

Moreover, Lee et al. (2010) used conditions with varied target numbers and target locations and found that prior response information, like the certainty about the hemifield in which the target will appear, might play an important role. Furthermore, they presumed the failure or success of a correct anti-saccade to be the result of a competition between the execution of a correct anti-saccade or an erroneous pro-saccade (see also Massen, 2004), depending on which process reaches its threshold first (see also Munoz & Everling, 2004). Nevertheless, if participants were instructed to delay their response until they were absolutely sure about the target location, latencies increased but error rate decreased compared to conditions in which the participants were

told to either respond as quickly as possible or as accurately as possible (Taylor & Hutton, 2009).

Regarding latencies, Smyrnis et al. (2002) found a mean latency for correct anti-saccades of 264 ms and a mean latency for incorrect pro-saccades of 197 ms. Likewise, Olk and Kingstone (2003) reported of longer reaction times in anti-saccade trials compare to pro-saccade trials. Moreover, they found mean reaction times for correct saccades towards a target in pro-saccade trials that were similar to the latencies of the incorrect pro-saccades in anti-saccade trials Smyrnis et al. (2002) had observed. However, other studies did not find any latency differences between correct anti- and pro-saccades (e.g. Lui et al., 2010).

Although oculomotor performance is greatly influenced by the task instruction and design, most studies agree that the standard anti-saccade task causes more errors than a pro-saccade task (e.g. Butler et al., 2009; Taylor & Hutton, 2009; Lee et al., 2010) and that latencies for correct anti-saccades are significant longer than for pro-saccades (e.g. Olk & Kingstone, 2003; Butler et al., 2009; Taylor & Hutton, 2009).

Various studies have reported of the involvement of different brain areas in anti-saccades. An increased activation for anti-saccades compared to pro-saccades was found in the dorsolateral prefrontal cortex (DLPFC), frontal eye field (FEF), anterior cingulate cortex (ACC), IPS and precuneus (Brown, Vilis & Everling 2007). Johnston and Everling (2006) also provided evidence for the DLPFC to transmit task relevant signals directly into the superior colliculus (SC) during anti-saccades. Furthermore, Connolly et al. (2000) reported of an inferior network in the IPS with greater IPS activity for anti-saccades compared to pro-saccades in the posterior superior parietal area and the middle inferior parietal area only showing activity during anti-saccades but not pro-saccades. An involvement of the IPS and FEF in anti-saccades was also found by Ettinger et al. (2008). Kunimatsu and Tanaka (2010) reported of an anti-saccade

activation in the thalamus and in agreement with these findings, abnormal activity in the thalamus was found in schizophrenia patients, who show an impairment in performing anti-saccades (Fukumoto-Motoshita et al., 2009). Finally, the role of the supplementary eye field (SEF) in eye movements that require a high level of intentional control has also been repeatedly investigated (Schlag-Rey et al., 1997; Olson & Gettner, 2002; Amador et al., 2004) and non-human studies on monkeys revealed an involvement of the SEF in anti-saccades (Schlag-Rey et al., 1997; Amador et al., 2004).

As explained above, anti-saccades appear to be driven by more complex processes that require greater effort than pro-saccades. In general the different assumptions about the cause of the increased error rates and the longer latencies for anti-saccades can be divided into two groups: While some research groups suggest a crucial role of vector inversion (Nyffeler et al. 2007), i.e. the ability to remap the target location to the opposite side, others assume that inhibition processes to withhold the reflexive saccade towards targets are more important (e.g. Olk et al., 2006).

2.1.1. Vector inversion in anti-saccades: remapping of the target location (off-line action)

To perform a correct anti-saccade, the participant has to inhibit the stimulus-driven pro-saccade but also has to be able to remap the target location to the opposite side to saccade towards the mirror location (Hallet, 1978; Connolly et al., 2000).

Indeed, Collins et al. (2008) identified the visual vector inversion as crucial for anti-saccades. The visual vector is described as the distance between the fixation point and target that first has to be computed to be successfully mirrored to the opposite side to finally execute a saccade towards the new location.

As the participant has to execute a saccade towards an imagined location and not directly towards the target, anti-saccades can be described as an off-line action. Other

off-line tasks include the performance of delayed responses towards a memorised target or pantomime actions. On the other hand, on-line actions are responses that are directed towards a present target, e.g. pro-saccades.

Various studies found evidence for off-line and on-line actions being processed by different structures (Milner & Goodale, 2006; Cohen et al., 2009). According to Milner and Goodale's theory, the ventral stream, which runs from the striate cortex to the inferior temporal cortex, is involved in off-line action, while the dorsal stream structures, which terminate in the PPC, process on-line actions (e.g. Ungerleider & Mishkin, 1982; Goodale & Milner, 1992; Milner & Goodale, 1995). For a detailed review about the dorsal and ventral visual stream please see also chapter 1.

The on-line – off-line dichotomy has been supported through research involving patients with optic ataxia, who generally have a lesion to the dorsal stream while their ventral stream remains intact, and through research conducted with visual form agnosia patient DF, who has a ventral stream lesion while her dorsal steam seems unaffected. In agreement with Milner and Goodale's model, optic ataxia patients show impairment in on-line actions like grasping an object but improve during an off-line task like a delayed grasping condition, when they can use the memorised characteristics of the target (Milner et al., 2001). Similarly patient DF is impaired in off-line actions like pantomime pointing (Carey et al., 2006) while she has no problem interacting with objects in the here and now, like adjusting her grip appropriately towards objects (Goodale, Jakobson & Keillor, 1994). Furthermore, in a small study Dijkerman, Milner and Carey (1997) tested DF briefly on anti- and pro-saccades. Again, as in pointing and grasping tasks, she showed impairments in anti-saccade generation (off-line) while she was able to execute pro-saccades correctly.

Stroke patients with hemispatial neglect tend to show a similar dissociation: For example Rossit, et al. (2008, 2011) found severe anti-pointing impairments in neglect

patients. Instead of pointing away from a target to the opposite direction, they pointed towards the target and in addition, the end-point accuracy of the correct anti-pointing movements was very low. On the other hand, no deficits for the pro-pointing condition, in which the patients pointed towards a target, were reported. Moreover, impairments for delayed reaches to left targets with a preserved ability to perform immediate reaching actions was found in patients with hemispatial neglect after right hemisphere stroke (Rossit et al., 2009b). Furthermore, Rossit et al. (2009a) found that the reduced accuracy in delayed leftward pointing was associated with lesions in the occipito-temporal cortex, in particular the superior, middle temporal gyri and the middle occipital and fusiform gyri. These findings are in line with Milner and Goodale's (2006) argument that patients suffering from spatial neglect may display problems in off-line processing similar to DF and that the areas damaged in these patients may display ventral stream properties.

More evidence for areas outside the ventral stream being involved in off-line actions comes from studies of the lateral occipital complex (LO), (e.g. Singhal, et al., 2006; Cohen, et al., 2009). Singhal, et al. (2006) found LO activation during stimulus presentation in a delayed reaching (and pointing) task and then a reactivation of this area during the response when no stimulus was visible. Furthermore, TMS applied to LO area influenced a grasp response only in the delayed condition of a grasping task (Cohen, et al., 2009). Interestingly, the LO area is damaged in patient DF (James et al., 2003). Thus, these findings are consistent with findings of DF's impairment in off-line tasks when she cannot act directly towards a stimulus.

These above reported studies give some evidence that on-line and off-line tasks require distinct actions that are processed by different brain areas.

2.1.2. Inhibition in anti-saccades

While many studies have found evidence that the remapping of the target location is a crucial process for the correct execution of an anti-saccade and I have argued that this can be regarded as an off-line action (see 2.1.1) Olk and Kingstone (2003) have suggested that the inhibition of the stimulus driven pro-saccade also plays an important role. They assume that this inhibition might be the main cause for longer anti-saccade latencies and that the remapping of the target has a minor influence only.

In fact frontal lobe structures have often been reported to be involved in saccadic inhibition processes (e.g. Guitton, Buchtel & Douglas, 1985; Hanes, Patterson & Schall, 1998). Studies on monkeys revealed fixation related neurons in the FEF which discharged during the fixation of a central spot while the activity of these cells paused before and during saccades (Hanes, Patterson & Schall, 1998).

Moreover, it is clear that anti-saccades not only require the ability of the individual to remap the target location towards the opposite side but also the ability to inhibit saccades towards a suddenly appearing stimulus. Indeed, it has been repeatedly found that patients with frontal lobe lesion show a higher error rate for anti-saccades (e.g. Guitton, Buchtel & Douglas, 1985; Pierrot-Deseilligny et al., 1991; Machado & Rafal, 2004; Ploner et al., 2005) while their pro-saccade performance appears normal (Guitton, Buchtel and Douglas, 1985).

Likewise, Meyniel et al. (2005) found that patients with fronto-temporal dementia as well as patients with progressive supranuclear palsey (PSP), which affects the DLPFC, were impaired in the inhibition of reflexive pro-saccades in delayed anti-saccade trials, and instead made anticipatory pro-saccades shortly after target presentation.

Further evidence for the contribution of the frontal lobe to saccade inhibition comes from studies with patients with mental health conditions like schizophrenia

(Reuter et al., 2007; Barton et al., 2008). It is known that schizophrenia patients show an abnormality in the prefrontal and temporal cortex (Goldstein et al., 1999; Gur et al., 2000; Fukumoto-Motoshita et al., 2009). While healthy participants showed greater DLPFC and thalamus activity during anti-saccades compared to pro-saccades (see also Brown, Vilis & Everling, 2007), no activity difference was found for schizophrenic patients, yet they showed very high overall activation in the brain areas studied (Fukumoto-Motoshita et al., 2009). Moreover, schizophrenia patients have shown high numbers of fixation losses and increased anti-saccade errors compared to healthy control subjects (Barton et al., 2008) and these authors argued that the findings are related to difficulties with saccade inhibition.

Evidence for the crucial role of the DLPFC in inhibition and voluntary eye movements comes also from non human primate studies. Wegener, Johnston and Everling (2008) applied microstimulation to the DLPFC of two monkeys which resulted in an increased error rate for ipsilateral anti-saccades, as well as longer reaction times for ipsilaterally directed pro- and anti-saccades. Complimentary results were also found by Nyffeler et al. (2007) who showed that TMS applied over the right DLPFC before target presentation caused a bilateral increase of error rates for anti-saccades. However, no significant increase of anti-saccade errors was observed when TMS was applied at the same time as the target or after target onset.

However, besides a contribution of frontal brain areas to inhibition processes, many studies agree that the SC, a midbrain oculomotor structure, plays a relevant role in the control of eye movements (Munoz & Wurtz, 1993; Munoz & Istvan, 1998; Johnston & Everling, 2006). Studies on monkeys found fixation cells in the rostral pole of the SC that discharged tonically during the active fixation of a fixation point but paused before and during saccades (Munoz & Wurtz, 1993; Munoz & Istvan, 1998). These results

appear to indicate that these fixation cells are part of a system which suppresses the generation of eye movements.

Further evidence for brain areas outside the frontal lobe being involved in inhibition comes from Butler et al. (2006). They reported a patient with a right temporo-parietal lesion who was unable to inhibit task irrelevant distractors. More importantly, in a recent study, Butler et al. (2009) reported a bilateral impairment in anti-saccade performance in patients with hemispatial neglect, with many erroneous pro-saccades being generated towards left and right targets. The classic lesion profile of such patients involves more posterior brain areas such as the right IPL (Mort et al., 2003) or the STG (Karnath, Ferber & Himmelbach, 2001). The problem with this experiment though is that it is not clear whether the reported impairments were inhibition or vector inversion (off-line action) problems. I will refer to this more in 2.1.4.

2.1.3. Purpose of the current experiment

Although neglect can occur after different lesion sites and a direct assignment to dorsal or ventral stream structures is difficult, Milner and Goodale (2006) claim that the dorsal stream remains relatively spared in neglect. Indeed, various studies have shown that neglect patients are able to perform on-line actions like pointing towards a target, which are supposed to be processed by the dorsal stream. For example Karnath, Dick and Konczalk (1997) found no impairment for neglect patients when they were asked to perform a simple pointing task. Moreover, even acute stroke patients with severe neglect could accurately reach to targets (Himmelbach & Karnath, 2003). Also, neglect patients seem to be able to calibrate their finger-thumb grip aperture correctly to grasp cylinders of different sizes (Pritchard et al. 1997; Milner, Harvey, & Pritchard, 1998) and they can make trajectory on-line corrections when the target suddenly changes position (Milner & Harvey, 2006; McIntosh et al., 2010).

Various studies have also found evidence for neglect patients to be impaired in off-line actions, which are not directly target-driven like delayed actions or anti-pointing. Rossit et al. (2009b) found that the delayed reaching performance of neglect patients was impaired for left targets while no problems occurred for immediate reaching. In line with this finding, Darling, Rizzo and Butler (2001) found an impairment of patients with lesions to the IPL, an area that is frequently damaged in neglect patients, for a delayed pointing task. Another off-line task is anti-pointing and it was found that again neglect patients show a severe impairment here while they seem not to be impaired for on-line pro-pointing actions (Rossit et al., 2011).

In summary, as predicted by Milner and Goodale (2006) who state that the dorsal stream remains relatively intact in neglect patients, they seem to be able to perform goal-directed, on-line responses. On the other hand they show deficits when performing off-line tasks and indeed, Milner and Goodale (1995) speculate that the IPL may get input from ventral stream regions, i.e. that input from the visual ventral may be inadequately processed. Moreover, Rossit et al. (2011) found further areas outside the ventral stream, namely the middle and superior temporal gyrus and the parahippocampal gyrus, that could also be implicated in the impaired anti-pointing performance. For more detailed information about neglect patients showing ventral stream type impairments, please see chapter 1.1.2.

While Rossit and colleagues (2008) have already found evidence for off-line impairments in neglect patients during anti-pointing, Butler et al. (2009) tackled the question by testing neglect patients with pro- and anti-saccades. Besides demonstrating an expected leftward impairment for pro-saccades (saccades falling too short) while right pro-saccades appeared normal, they reported bilateral deficits for anti-saccades. Butler and colleagues found that the patients produced a great number of erroneous pro-saccades in the anti-saccade task, i.e. they looked towards the target instead of away

from it, in the anti-saccade condition. Butler and colleagues suggested therefore, that the patients either had a problem in inhibiting the reflexive saccades or that they were impaired in remapping the target location to the opposite side.

In the current study I now aim to take a closer look at this question by testing the inhibition ability of stroke patients with neglect. In the first experiment I will test five stroke patients with neglect and 12 age-matched control subjects with a task that was adapted from Butler et al.'s (2009). In addition to Butler and his colleagues' pro- and anti-saccade condition, the patients will be presented with an additional fixation task (chapter 2.2.). However, this first fixation task is very simple as the same response is required throughout the blocks. Therefore, a second experiment will be carried out with a more difficult task to take more detailed look at eye movement inhibition (chapter 2.3.). Here I chose an interleaved design (i.e. I randomly mixed pro-saccade and fixation trials) that was adapted from Olk and Kingstone (2009). In contrast to the first experiment in which the participants know which response is required, in tasks with interleaved conditions the next trial is not predictable and therefore the participant is required to make a quick decision in order to respond correctly for each trial anew. Thus, this design provides a more demanding task to test the participants' ability to withhold an eye movement.

Regarding the assumption that neglect patients show a similar impairment for off-line actions like patient DF, I expect them to show deficits in the anti-saccade conditions of experiment 1. Like Butler et al. (2009) I expect them to make erroneous pro-saccades towards the target instead of looking away. Moreover, I expect them to be able to inhibit reflexive saccades in the fixation trials of experiment 1 as well as in the more difficult interleaved conditions of experiment 2. This inhibition ability would support the view whereby anti-saccade errors might be caused by a problem to remap the target location to the opposite side, i.e. performing an off-line action, rather than

being it an inhibition impairment. Furthermore, the patients' ability to inhibit eye-movements while still making anti-saccades errors, would give further evidence for the claim that brain areas that are effected in neglect patients show ventral stream properties and possibly cause problems with off-line actions.

2.2. Experiment 1: Anti-saccades, pro-saccades and fixation

Rossit et al. (2008) found anti-pointing impairments for neglect patients which is in line with Milner and Goodale's statement that the IPL, an area frequently damaged in neglect, is connected to the ventral stream. Likewise Butler et al. found bilateral errors for anti-saccades. However, as the lesion locations of neglect patients vary, a direct explanation in terms of anatomy will remain difficult. Therefore I will try to approach this question in terms of function. Can neglect patients perform anti-saccades and if not is this due to impaired inhibition or vector inversion (off-line action)?

For my first experiment all participants will be tested with Butler et al.'s (2009) previously used pro-saccade and anti-saccade tasks. The task is identical to Butler and his colleagues but additionally, the patients will be presented with a simple fixation task that is adapted from the pro- and anti-saccade conditions. It consists of a central fixation point and a suddenly appearing peripheral target but here, the participants have to inhibit all eye movements and maintain fixation on the central point when the target appears.

I expect neglect patients to show the same leftward errors for pro-saccades and bilateral errors for anti-saccades which Butler et al. (2009) reported. Furthermore, if an impairment in the fixation task is observed, with erroneous pro-saccades generated towards the target, this could be taken as evidence for an inhibition problem and explain the bilateral anti-saccade errors. However, if the patients are able to withhold reflexive saccades in the fixation condition, an inability to remap the target location to the opposite side (i.e. to perform an off-line action) would be a more parsimonious explanation for the bilateral anti-saccade errors.

2.2.1. Method

Healthy participants

12 healthy elderly right-handed subjects (mean age 73.2 years, SD 5.1) participated in the study and were reimbursed for travel expenses.

Patients

Five male stroke patients (mean age 67.8 years, SD 7.2) with hemispatial neglect took part in the study (see table 2.1 for demographic and clinical details). The patients were assessed with the BIT (Wilson, Cockburn & Halligan, 1987) and none of them scored above the BIT cut-off of 129, indicating they all suffered from hemispatial neglect.

Next a computer based perimetry test was presented on a laptop to assess possible visual field deficits. A black stimulus (circle with 2 mm of diameter) appeared for 100 ms in one of 36 possible locations on a white background. The distance between the targets was fixed (6.5 degrees in x-axis and 4.8 degrees in the y-axis). Patients were asked to press a key when they detected its appearance while fixating on a central cross that would disappear at stimulus onset. A total of 106 trials (including 10 practise and 24 catch trials) were presented, two per target position. Three patients were examined with this test and only one of them showed evidence of a visual field deficit. A further two patients were unable to complete the hemianopia test as they were not able to detect any of the small target dots at all.

Patients were recruited from the Southern General Hospital in Glasgow. The study was conducted in accordance with the ethical guidelines of the South Glasgow University Hospitals NHS Trust and the Declaration of Helsinki. All participants gave their informed consent prior to the study.

Table 2.1: Demographic and clinical data of the right brain-damaged patients with hemispatial neglect.

PATIENT	GENDER	AGE	SCAN	ETIOLOGY	LESION LOCATION	TIME SINCE INJURY ONSET	VISUAL FIELD DEFICIT	BIT
JS	M	74	MRI	Infarct	Temporal, insular cortex and periventricular white matter	6	YES	117
JCA	M	63	MRI	Infarct	Superior post-central gyrus (parietal lobe) and occipital	3	NO	93
JQ	M	59	MRI	Haematoma	Basal ganglia	3	-	35
JM	M	67	MRI	Infarct	Frontal, basal ganglia	38	-	61
TH	M	76	CT	Infarct	Temporo-parietal	31	NO	126

(BIT = Behavioural Inattention Test cut-off = 129)

Apparatus and stimuli

A white circle with a diameter of 0.6 degrees was displayed centrally on a black background and served as a fixation point. Target stimuli consisted of a single white square of 0.6 degrees. In each trial this square would appear peripherally on the horizontal meridian at either 7.3 degrees to the left or the right of the fixation circle. Targets were adapted from Butler et al. (2009).

The tasks were presented on a 17" SVGA monitor with 800 x 600 pixel resolution and 74 Hz refresh rate. The monitor was located at 57 cm from the chinrest. A second PC was used to record eye position data on-line. Eye movements were monitored with the SMI EyeLink System (SensoMotoric Instruments GmbH, Teltow, Germany). The system uses the centre of the pupil and the corneal reflection technique to define pupil position. Eye movements were recorded at 250 Hz, with an operational spatial resolution of about 0.3º. Saccade onset was defined as a change in eye position with a minimum velocity of 35º/s or a minimum acceleration of 9500º/s^2.

Procedure

The experimental task consisted of three blocks with 80 trials each: Anti-saccade condition, pro-saccade condition and fixation condition.

Each block started with a 10-trial-demonstration to explain the task. Then a nine-point grid calibration and validation procedure was carried out in which the participants were asked to saccade to a white, circular disk (identical to the fixation point). This appeared sequentially (but unpredictably) in a 3x3 grid. After a satisfactory validation had been obtained, a block of trials was run.

At the beginning of each trial, participants were instructed to fixate the central dot until they kept their eyes steady on this fixation point, which could be seen on the second computer screen. The task was then started manually via button press. After a

random interval between 500 – 1,500 ms a single white box appeared peripherally either at the right or the left side of the fixation point for 1,000 ms while the fixation dot remained visible. Each trial ended with the disappearance of the central dot and the box and then a new fixation point appeared in the centre of the screen.

In the pro-saccade condition the participants were asked to make an eye movement towards the peripherally appearing box as quickly and accurately as possible. In the anti-saccade condition participants were instructed not to look at the peripherally white square when they detected it on the screen, but to look to the same location on the opposite side as quickly as possible. For the fixation condition the participants were instructed to ignore the peripheral box and maintain fixation on the fixation point.

Each participant had to complete all three blocks. An equal number of left and right targets were presented in random order within each blocks and the block sequence was counterbalanced. Example displays are shown in figure 2.1.

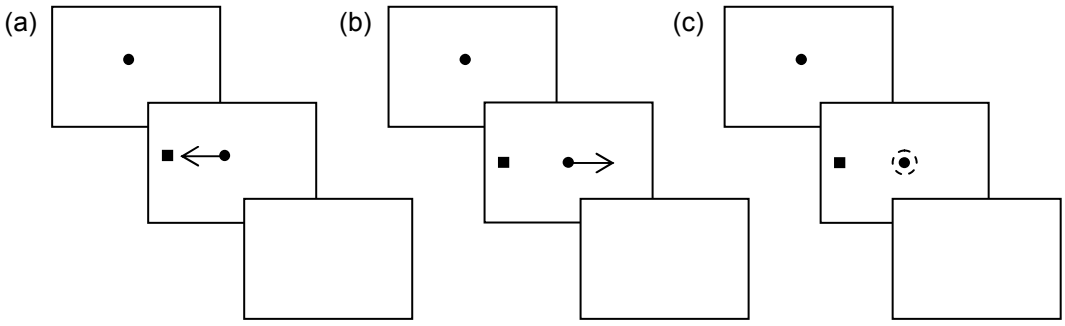


Fig. 2.1: Schematic layout of the pro-saccade, anti-saccade and fixation condition. In the pro-saccade condition (a), the participant was required to initiate a saccade towards the square as quickly and as accurately as possible. In the anti-saccade condition (b) the participant had to look in the opposite direction, and in the fixation condition (c) the participant had to maintain fixation on the central dot while the square was presented on the left or right side.

Data processing

In the pro- and anti-saccade condition I excluded trials in which the participant failed to initiate an eye movement. Next I identified the first saccade after stimulus onset for the further analyses. Furthermore, I excluded trials in which a saccade with latencies shorter than 80 ms after stimulus onset was made, as these were considered anticipatory. Trials in which the central circle was not properly fixated at the beginning of the trial (deviation larger than 1 degree) were also excluded from analyses, as well as pro- and anti-saccade trials with saccades amplitudes shorter than 1 degree.

These criteria resulted in a rejection of 33.5% of the anti-saccade trials with left targets and 27.5% of right target trials for the neglect patients and 6.9% and 10.8% respectively for the healthy controls. For the pro-saccade condition 39% of left target trials and 34.8% of right target trials were excluded for the neglect patients, while 9.2% and 11.3% of the trials for healthy controls were rejected. Finally, 12.8% of the left target fixation trials were excluded for the patients and 10.8% of the trials with right targets. For the healthy controls I excluded 3.1% of left target fixation trials and 5.4% of the right target trials. Detailed information for each exclusion category can be found in table 2.2.

Table 2.2: Percentage of excluded trials for the anticipation, fixation and amplitude criteria, for anti-saccades, pro-saccades and fixation trials, broken down into left and right targets and presented separately for controls and neglect patients. The amplitude criterion was not applicable for fixation trials.

		Anti-saccades		**Pro-saccades**		**Fixation**	
		Left	**Right**	**Left**	**Right**	**Left**	**Right**
Controls	**anticipation**	3.1%	6.7%	4.4%	6.9%	1.9%	3.5%
	fixation	1.7%	3.1%	4%	2.9%	1.3%	1.9%
	amplitude	2.1%	1%	0.8%	1.5%	-	-
Neglect	**anticipation**	12%	11.3%	9.5%	14.8%	8%	5.8%
	fixation	12.5%	14.3%	17.3%	17.5%	4.8%	5%
	amplitude	9%	2%	12.3%	2.5%	-	-

2.2.2. Results

For the analyses only the first saccade after stimulus onset was used in most cases. However, to investigate if the participants had understood the task even if they had made a first saccade in the wrong direction during anti-saccade trials, I also looked at the second saccade to assess if a corrective eye movement in the required direction was executed. The statistical analyses were done with the Statistical Package for the Social Sciences (SPSS) using repeated measures analysis of variance (ANOVA) and post-hoc pairwise comparisons were done with Bonferroni adjustment ($p<.05$). To take a closer look at the individual data for some of the variables, a modified t-test (Crawford & Howell, 1998) was used. This test allows the comparison of a single patient to a sample of control subjects. Finally, we wanted to assess if there was a correlation between the fixation and anti-saccade performance as both tasks are supposed to require inhibition processes. Due to the low number of data points, Spearman's rho correlations were employed.

2.2.2.1. Pro-saccades

The *absolute angular error* and the *saccade reaction time* (SRT) were calculated for all pro-saccade trials.

To identify the accuracy of a saccade, the *absolute angular error* was calculated as the distance between the landing point of the first saccade after stimulus onset and the actual stimulus location, using only the X-coordinates (see also Butler et al., 2009). The absolute angular error only looked at the accuracy of a saccade but did not take into account if a saccade over- or undershot the target location.

The results showed that all controls were able to make an accurate eye movement towards targets on both sides. For the pro-saccades to the left they had an

error of .55 degrees and a standard deviation (SD) of .2; for right targets the error was .73 degrees (SD .2). Neglect patients were worse on this task, in particular when pro-saccades towards left targets were required (absolute angular error 3.01 degrees, SD 1.6). Their errors towards right targets were 1.28 degrees (SD .4). For a detailed listing of all group and individual data please see table 2.4.

A 2x2 mixed ANOVA (table 2.3) for the dependent variable *Absolute Angular Error* with *group* as a between-subject factor and *side* of target as the within-subject factor revealed main effects of *side* ($F_{(1,15)} = 11.7$, $p<.01$) and *group* ($F_{(1,15)} = 38.4$, $p<.001$). This was qualified by the significant *side x group* interaction ($F_{(1,15)} = 17.8$, $p<.001$).

Table 2.3: ANOVA with the factors side and group for Absolute Angular Error of correct pro-saccades. Significant main effects and/or interaction in italic.

		df	F	Sig.
Within-Subjects Effect	***Side***	*1*	*11.648*	*< .004*
	Side x Group	*1*	*17.84*	*< .001*
	Error (Side)	15		
Between-Subjects Effect	***Group***	*1*	*38.404*	*< .001*
	Error	15		

df = degrees of Freedom; F = F-Value, Sig. = significance level.

Pairwise comparisons showed that neglect patients' pro-saccade accuracy was significant worse compared to healthy controls for left ($p<.001$) and right ($p<.001$) targets (fig. 2.2). Furthermore, a significant difference was observed between right and left targets for neglect patients ($p<.001$), with accuracy for left targets being worse than that of right targets (fig. 2.3). There was no significant difference between left and right targets for the healthy controls.

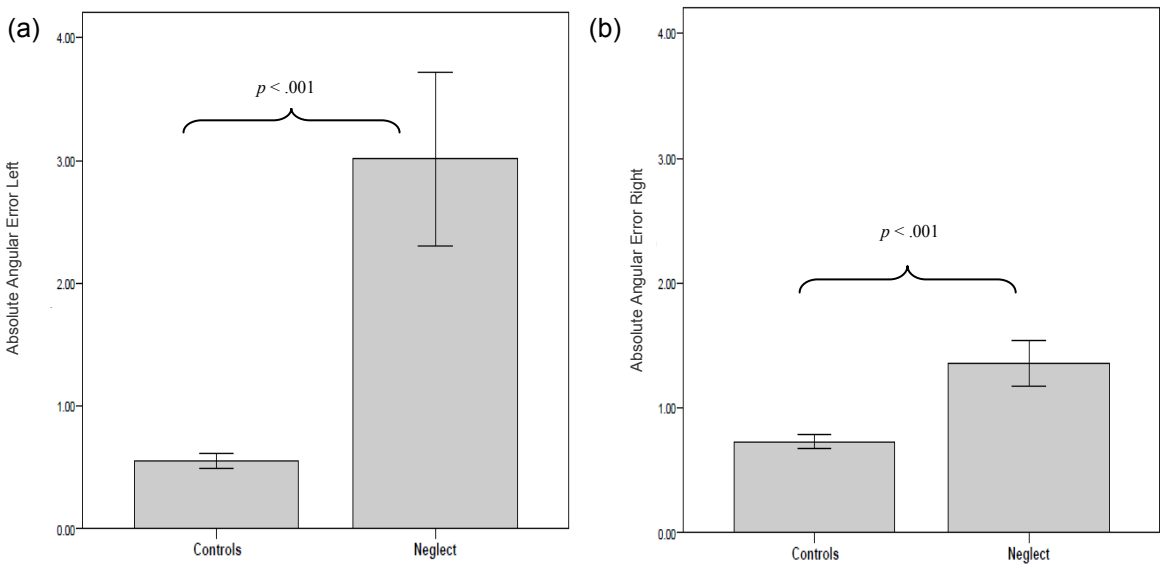


Fig. 2.2: Mean Absolute Angular Error in degrees of correct pro-saccades for controls and neglect patients for left (a) and right (b) targets. Error bars show +/- 1 standard error (SE).

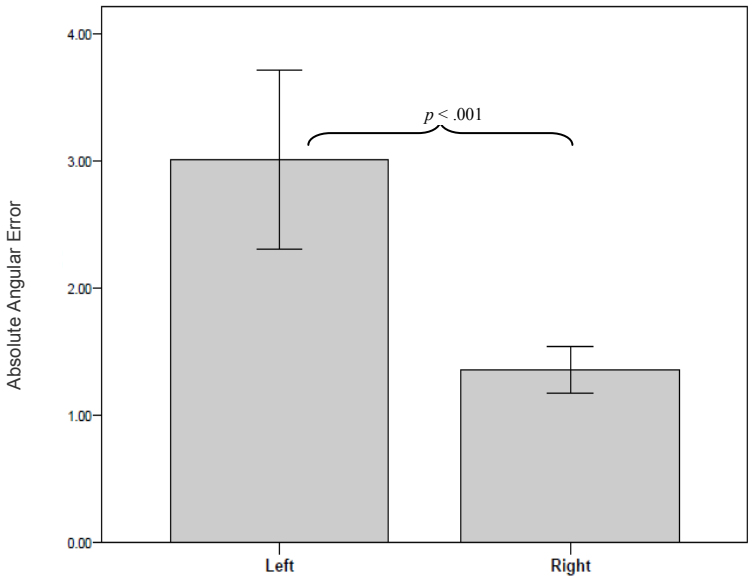


Fig 2.3: Mean Absolute Angular Error in degrees of correct pro-saccades for neglect patients for left and right targets. Error bars show +/- 1 SE.

On an individual level (see also table 2.4), only TH was not impaired while all other patients showed deficits (JCA, JQ, JM: $p<.001$; JS: $p<.01$, two-tailed) for left targets compared to the healthy controls. For right targets, JQ and JS performed perfectly, while the other three patients were slightly impaired (JCA and TH: $p<.05$; JM: $p<.01$, two-tailed).

Table 2.4: Absolute Angular Error in degrees of correct pro-saccades for left and right targets; group means and individual data for neglect patients.

	Absolute Angular Error [degrees] target left	**Absolute Angular Error [degrees]** target right
Controls	0.55 (SD 0.2)	0.73 (SD 0.2)
Neglect	3.01 (SD 1.6)	1.28 (SD 0.4)
JS	2.11	0.98
JCA	3.33	1.60
JQ	4.54	0.94
JM	4.32	1.91
TH	0.77	1.36

Finally a closer look was taken at the *SRT* and another mixed ANOVA with *group* as between-subject factor and *side* of target as the within-subject factor was conducted (table 2.5). A significant main effect was found for the factor *side* ($F_{(1,15)}$ = 9.2, p<.01). This was qualified by a significant interaction of *side x group* ($F_{(1,15)}$ = 13.8, p<.01).

Table 2.5: ANOVA with the factors side and group for SRT of pro-saccades. Significant main effects and/or interaction in italic.

		df	**F**	**Sig.**
Within-Subjects Effect	***Side***	*1*	*9.204*	*.008*
	Side x Group	*1*	*13.794*	*.002*
	Error (Side)	15		
Between-Subjects Effect	**Group**	1	.361	.557
	Error	15		

Pairwise comparisons revealed a significant difference between right and left targets for neglect patients (p<.001) with significantly faster saccades towards right targets (193 ms, SD 50.6) compared to left targets (281 ms, SD 37.1) (fig 2.4). No difference between left and right targets was found for healthy controls (SRT for left targets: 214 ms, SD 61.2; saccadic reaction time for right targets: 223 ms, SD 65.6). Furthermore a significant difference was found between neglect patients and healthy

controls for pro-saccades towards left targets (p<.05) with neglect patients showing longer latencies (fig 2.5). There was no significant difference between the groups for right targets.

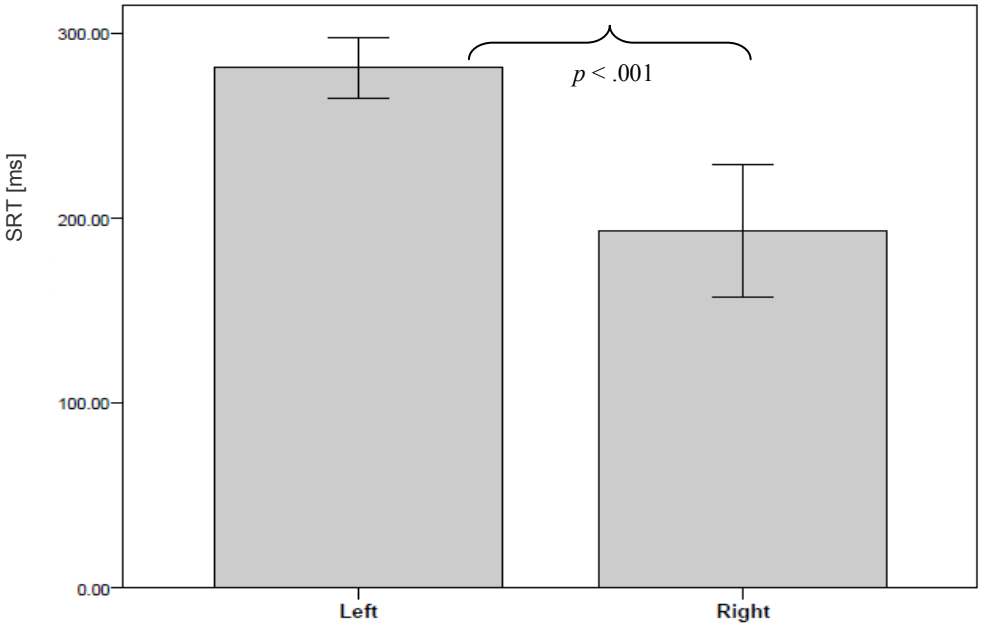


Fig. 2.4: Mean SRT of correct pro-saccades for neglect patients for left and right targets. Error bars show +/- 1 SE.

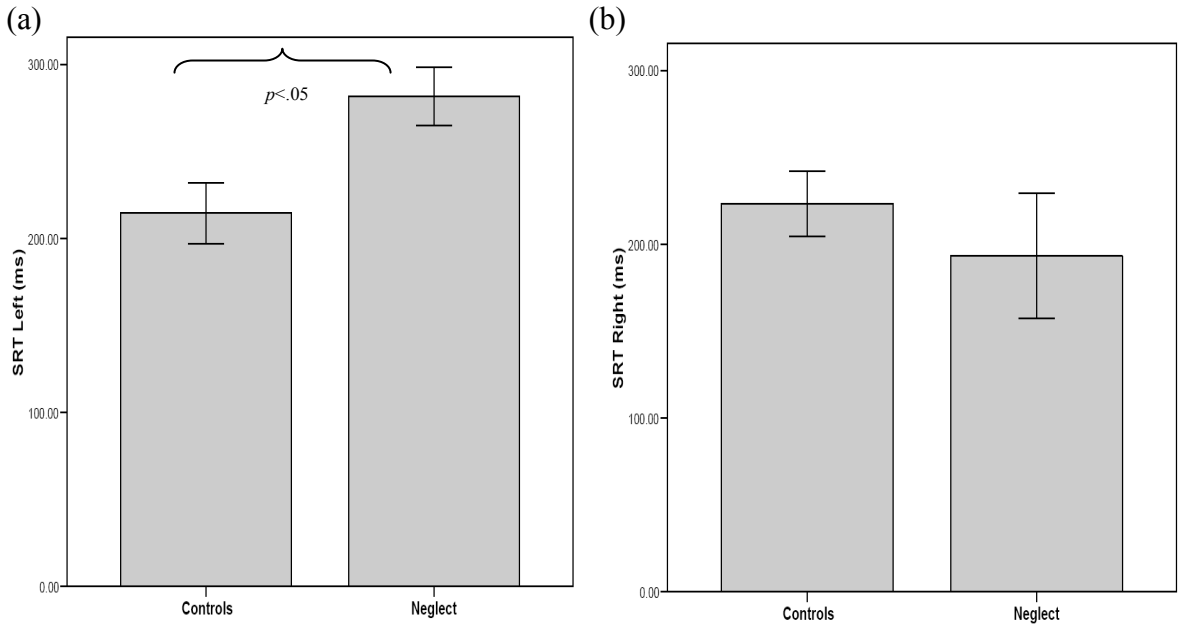


Fig. 2.5: Mean SRT of correct pro-saccades for controls and neglect patients for left (a) and right (b) targets. Error bars show +/- 1 standard error (SE).

However, on an individual level no patient showed longer latencies compared to the healthy controls for left and right targets (all patients $p>.05$, two-tailed). For individual data, please see table 2.6.

Table 2.6: SRT in milliseconds (ms) of correct pro-saccades for left and right targets; group means and individual data for neglect patients.

	SRT [ms] target left	**SRT [ms]** target right
Controls	214 (SD 61.2)	223 (SD 65.6)
Neglect	281 (SD 37.1)	193 (SD 50.6)
JS	244	115
JCA	299	302
JQ	336	171
JM	274	128
TH	254	250

2.2.2.2. Anti-saccades

For the anti-saccades I calculated the *percentage of correct trials*. A trial was identified as correct, when the participant had been able to inhibit the stimulus driven saccade towards the peripheral target and instead initiated a saccade in the opposite direction by at least two degrees. I also calculated the *absolute angular error* of the correct anti-saccades, the *SRT of the correct anti-saccades* and *erroneous pro-saccades*, as well as the *proportion of corrected anti-saccades* after a false pro-saccade. For the latter I looked at the second saccade in trials in which an erroneous pro-saccade occurred, i.e. when the first saccade was falsely made towards the target stimulus instead of away from it, the second saccade that was executed immediately after the first on was examined. If this second saccade was then made into the correct direction, i.e. away from the target to the mirrored location, the trial was defined as *corrected*.

For the amount of correct saccades, Neglect patients were more impaired than healthy controls with only 38% (SD 31.4) correct responses to left targets and 43% (SD

41.7) correct responses to right targets, while healthy controls reached 88% (SD 10.6) and 86% (SD 12.7) respectively (for all group and individual data see table 2.8).

A 2x2 mixed ANOVA (table 2.7) with *group* as between-subjects factor and *side* of target as within-subjects factor was carried out. Only, a main effect for *group* was found ($F_{(1,15)}$ = 18.7, p<.001), indicating significantly greater errors for neglect patients than the healthy controls for both left and right targets (fig. 2.6).

Table 2.7: ANOVA with the factors side and group for percentage of correct anti-saccades. Significant main effects and/or interaction in italic.

		df	F	Sig.
Within-Subjects Effect	**Side**	1	14.598	< .730
	Side x Group	1	96.840	< .379
	Error (Side)	15		
Between-Subjects Effect	***Group***	*1*	*18.691*	*< .001*
	Error	15		

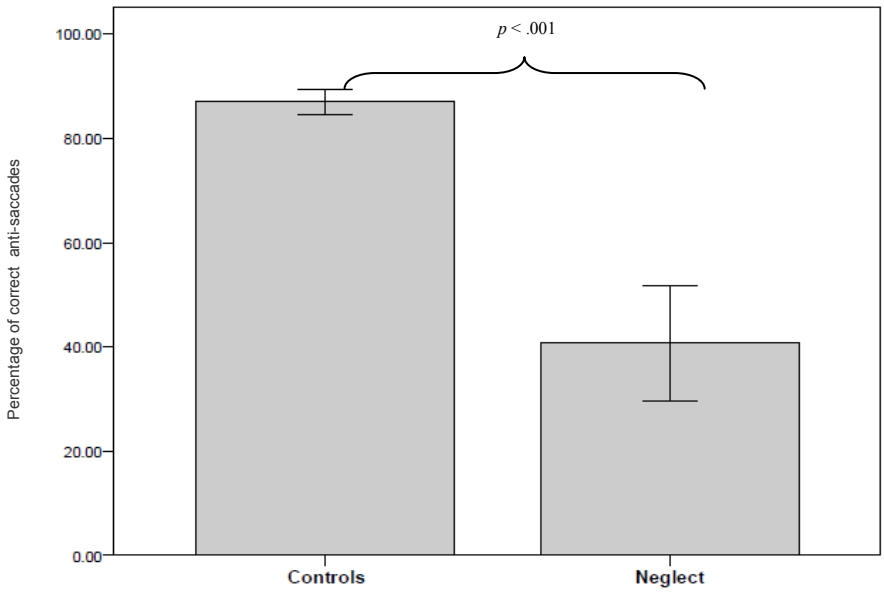


Fig. 2.6: Percentage of correct anti-saccades for controls and neglect patients. Error bars show +/- 1 SE.

Looking at the individual scores, Crawford and Howell's modified t-test revealed that two (JCA, TH) out of the five patients showed surprisingly good performance on anti-saccades away from the right target (both $p>.05$; two-tailed) and TH also performed perfectly for left targets ($p>.05$; two-tailed). Please see table 2.8 and figure 2.7 for the individual scores.

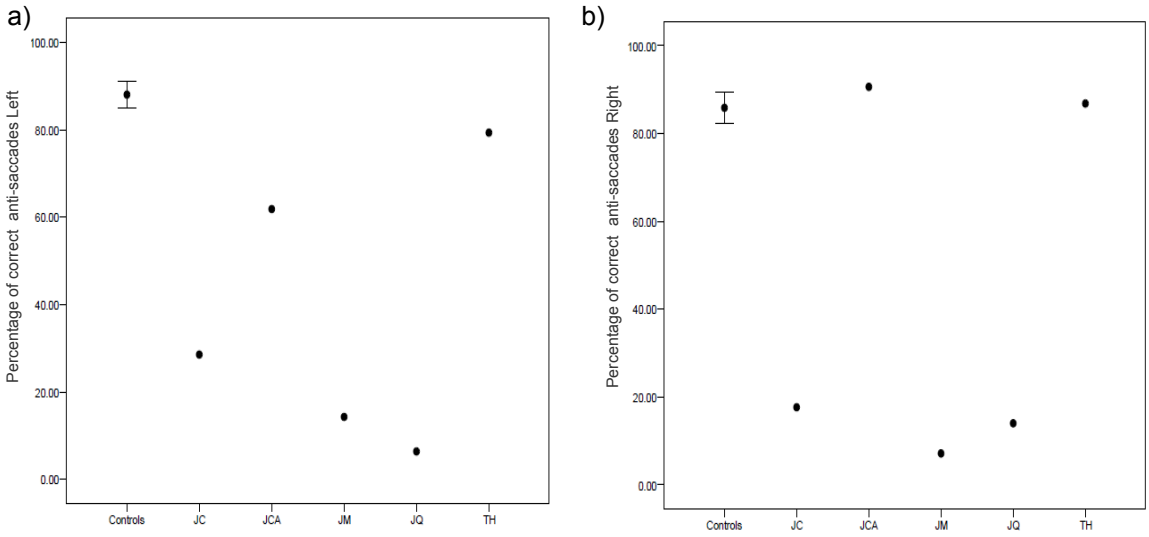


Fig. 2.7: Percentage of correct anti-saccades for controls (mean) and neglect patients (individual data) for left (a) and right (b) targets. Error bars show +/- 1 SE.

Table 2.8: Percentage of correct anti-saccades for left and right targets; group means and individual data for neglect patients.

	correct anti-saccades [%] target left	**correct anti-saccades [%]** target right
Controls	88 (SD 10.6)	86 (SD 12.7)
Neglect	38 (SD 31.4)	43 (SD 41.7)
JS	29	18
JCA	62	91
JQ	6	14
JM	14	7
TH	70	87

Next the *absolute angular error* was calculated to measure the accuracy of the anti-saccade. It was calculated as the distance between the end of the saccade and the location exactly opposite the actual stimulus in the horizontal plane. It was again based on the X-coordinates (see also Butler et al., 2009) and did not take into account if a saccade over- or undershot the goal location. Only correct anti-saccade trials were analysed for the absolute angular error.

A 2x2 mixed ANOVA with *group* as between-subjects factor and *side* of target as within-subjects factor was calculated and a main effect of *group* ($F_{(1,15)} = 14.1$, $p<.01$) was found only (table 2.9). The correct anti-saccades of neglect patients were less accurate compared to the healthy subjects (fig 2.8). The expected saccade endpoint was missed by 4.56 degrees (SD 2.4) for left targets and 4.49 degrees (SD 1.8) when the target appeared on the right side. Anti-saccades of healthy controls were much more accurate with an absolute angular error of 2.39 degrees (SD 0.7) and 2.04 degrees (SD 0.7) for leftwardly and rightwardly presented targets.

Table 2.9: ANOVA with the factors side and group for the Absolute Angular Error of correct anti-saccades. Significant main effects and/or interaction in italic.

		df	F	Sig.
Within-Subjects Effect	**Side**	1	.782	.390
	Side x Group	1	.139	.575
	Error (Side)	15		
Between-Subjects Effect	***Group***	*1*	*14.12*	*.002*
	Error	15		

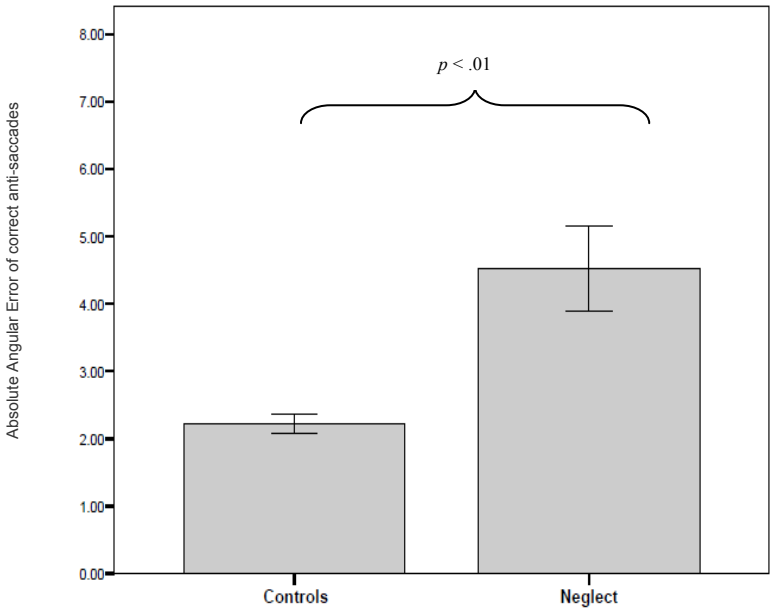


Fig. 2.8: Mean Absolute Angular Error in degrees of correct anti-saccades for controls and neglect patients. Error bars show +/- 1 SE.

Again on an individual level (see also table 2.10 and fig. 2.9), patient TH as well as patient JCA showed very good accuracy for anti-saccades to both sides that did not differ from the control group (both $p>.05$ for left and right targets; two-tailed).

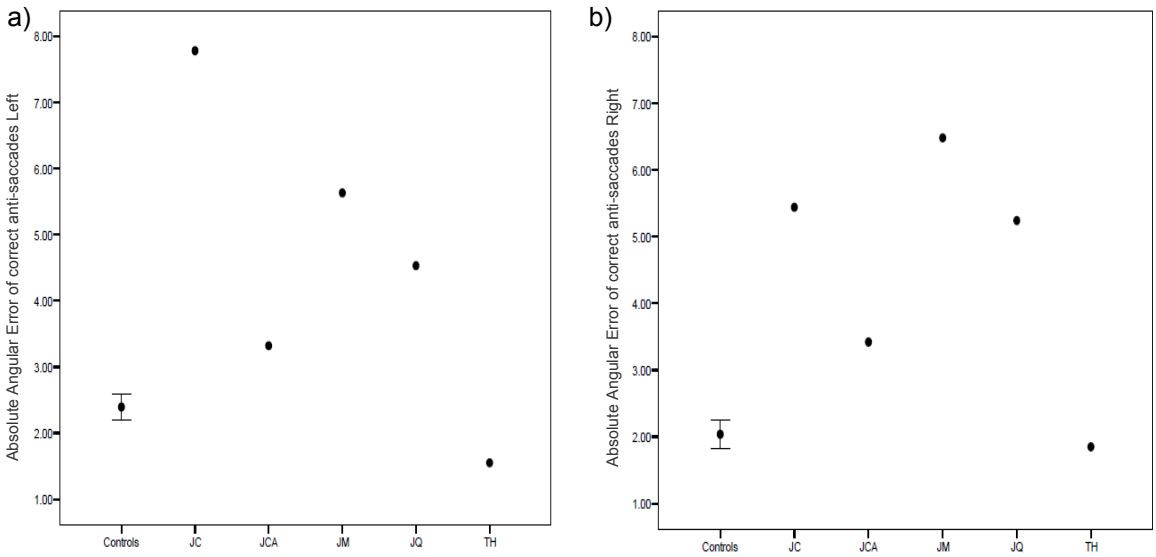


Fig. 2.9: Absolute Angular Error in degrees of correct anti-saccades for controls (mean) and neglect patients (individual data) for left (a) and right (b) targets. Error bars show +/- 1 SE.

Table 2.10: Absolute Angular Error of correct anti-saccades in degrees for left and right targets; group means and individual data for neglect patients.

	Absolute Angular Error [degrees] target left	Absolute Angular Error [degrees] target right
Controls	2.39 (SD 0.7)	2.04 (SD 0.7)
Neglect	4.56 (SD 2.4)	4.49 (SD 1.8)
JS	7.78	5.44
JCA	3.32	3.42
JQ	4.53	5.24
JM	5.63	6.48
TH	1.55	1.85

I next examined the *SRT* of the correct anti-saccades. Another 2x2 mixed ANOVA with *group* as a between-subjects factor and the *side* of target as a within-subjects factor was conducted. No significant effects were found (table 2.11). With mean latencies of 373 ms (SD 169.3 ms) for left targets and 335 ms (SD 175.7 ms) for right targets the neglect patients did not significantly differ from the healthy controls (359 ms for left targets, SD 79.9 ms; 369 ms for right targets, SD 49.9 ms).

Table 2.11: ANOVA with the factors side and group for the SRT of correct anti-saccades.

		df	F	Sig.
Within-Subjects Effect	**Side**	1	.432	.521
	Side x Group	1	1.259	.280
	Error (Side)	15		
Between-Subjects Effect	**Group**	1	.034	.858
	Error	15		

On an individual level only patient JCA was observed to be particularly slow on both sides (left targets: 655 ms, $p<.01$, two-tailed; right targets: 570 ms, $p<.01$, two-tailed). Please see table 2.12 for all the individual and group data.

Table 2.12: SRT of correct anti-saccades in ms for left and right targets; group means and individual data for neglect patients.

	SRT [ms] target left	**SRT [ms]** target right
Controls	359 (SD 79.9)	369 (SD 49.9)
Neglect	373 (SD 169.3)	335 (SD 175.7)
JS	397	389
JCA	655	570
JQ	231	313
JM	277	80
TH	304	325

Next I examined the *SRT of the erroneous pro-saccades* in the anti-saccade condition. A 2x2 mixed ANOVA (table 2.13) with *group* as a between-subjects factor and the within-subjects factor *side* of target revealed only a highly significant main effect for *side* ($F_{(1,13)}$ = 16.7, p<.001) with slower erroneous pro-saccades for right compared to leftward targets (fig. 2.10). Only patient JCA failed to show this pattern and had longer reaction times when saccading towards right targets. Furthermore, two control participants did not execute any erroneous pro-saccades, so only data of ten healthy controls could be processed for this part of the analysis. Table 2.14 shows the individual data of all patients as well as the group data.

Table 2.13: ANOVA with the factors side and group for the SRT of erroneous pro-saccades in the anti-saccade condition. Significant main effects and/or interaction in italic.

		df	**F**	**Sig.**
Within-Subjects Effect	***Side***	*1*	*16.693*	*.001*
	Side x Group	1	.432	.522
	Error (Side)	13		
Between-Subjects Effect	**Group**	1	4.251	.06
	Error	13		

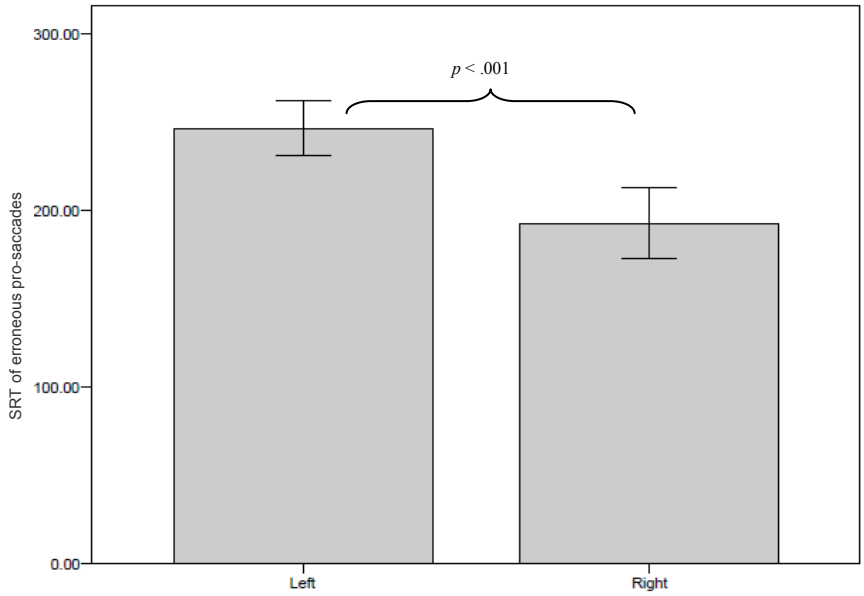


Fig. 2.10: Mean SRT for erroneous pro-saccades in the anti-saccade condition for neglect patients for left and right targets. Error bars show +/- 1 SE.

Table 2.14: SRT for erroneous pro-saccades in ms in the anti-saccade condition for left and right targets; group means and individual data for neglect patients.

	SRT [ms] target left	**SRT [ms] target right**
Controls	226 (SD 66.2)	193 (SD 89.3)
Neglect	284 (SD 37.5)	185 (SD 69.9)
JS	294	121
JCA	291	299
JQ	323	175
JM	222	138
TH	292	193

To ensure the patients had understood the task, I looked at the *percentage of corrected anti-saccades* after an erroneous pro-saccade occurred. Again, only the data of ten controls were included in this analysis (see also SRT for erroneous pro-saccades). The 2x2 mixed ANOVA with *group* as a between-subjects factor and the within-subjects factor *side* of target revealed significant main effects for *side* ($F_{(1,13)}$ = 8.1, p<.05) and *group* ($F_{(1,13)}$ = 5.8, p<.05) (table 2.15). The healthy control participants corrected most of their erroneous pro-saccades (84% for left targets, 91% for right

targets), while the neglect patients corrected less, in particular when the target had appeared on the left side (52% for left targets, 79% for right targets).

Table 2.15: ANOVA with the factors side and group for the corrected anti-saccades. Significant main effects and/or interaction in italic.

		df	F	Sig.
Within-Subjects Effect	***Side***	*1*	*8.046*	*.014*
	Side x Group	1	2.796	.118
	Error (Side)	13		
Between-Subjects Effect	***Group***	*1*	*5.832*	*.031*
	Error	13		

On an individual level (see also table 2.16) only two patients were impaired to correct erroneous pro-saccades when the target appeared on the left side: JS ($p<.05$, two-tailed) and JM ($p<.01$, two-tailed). Both corrected a greater number of saccades when the target was presented on the right side, but JS still performed worse than the control group ($p<.01$, two-tailed). Furthermore, JCA, who was not impaired for left targets ($p>.05$, two-tailed) showed a reduced percentage of corrected anti-saccades when the target was presented on the right side ($p<.05$, two-tailed). TH's performance was perfect and, as in addition to his already high percentage of correct anti-saccades, he also corrected all erroneous pro-saccades that had occurred.

Table 2.16: Percentage of corrected anti-saccades after an erroneous pro-saccades occurred for left and right targets; group means and individual data for neglect patients.

	corrected anti-saccades [%] target left	**corrected anti-saccades [%]** target right
Controls	84 (SD 18.6)	91 (SD 10.5)
Neglect	52 (SD 35)	79 (SD 18.2)
JS	32	57
JCA	50	67
JQ	68	95
JM	8	77
TH	100	100

2.2.2.3. Fixation

For the fixation trials I calculated the *percentage of correct trials*. A trial was passed when the participant maintained fixation for the duration of the trial and made no saccade bigger than 1 degree. Only deviations in the X-coordinates were considered indicative of inhibition failure. Vertical drifts were deemed not to be stimulus driven.

All healthy controls were able to inhibit eye movements almost perfectly with mean percentages of correct trials of almost 100% (SD 1.1) for leftwardly presented targets and 99% (SD 2.1) for rightwardly presented targets. Neglect patients were also generally able to inhibit the stimulus driven eye movement but nevertheless a greater number of incorrect pro-saccades were generated to targets on both sides with a mean percentage of correct trials of 88% (SD 25.6) for left targets and 80% (SD 31.6) for right targets.

A mixed ANOVA with *group* as the between-subject factor and *side* of target as the within-subject factor was carried out which revealed a significant main effect for s*ide* ($F_{(1,15)} = 7.1$, $p<.05$), which was also qualified by the significant interaction of *side x group* ($F_{(1,15)} = 18.7$, $p<.05$) (table 2.17). Post hoc comparisons showed a significant difference between neglect patients and healthy controls for rightwardly presented targets ($p<.05$) with neglect patients making more erroneous pro-saccades towards right targets. No difference between the groups was found for left targets (fig. 2.11). Furthermore a significant difference was found between right and left targets for neglect patients ($p<.01$) with more false pro-saccades towards right targets (fig. 2.12). For healthy controls, no significant difference was found between rightwardly and leftwardly presented targets.

Table 2.17: ANOVA with the factors side and group for percentage of correct fixation. Significant main effects and/or interaction in italic.

		df	F	Sig.
Within-Subjects Effect	***Side***	*1*	*7.083*	*.018*
	Side x Group	*1*	*6.107*	*.026*
	Error (Side)	15		
Between-Subjects Effect	**Group**	1	3.844	.069
	Error	15		

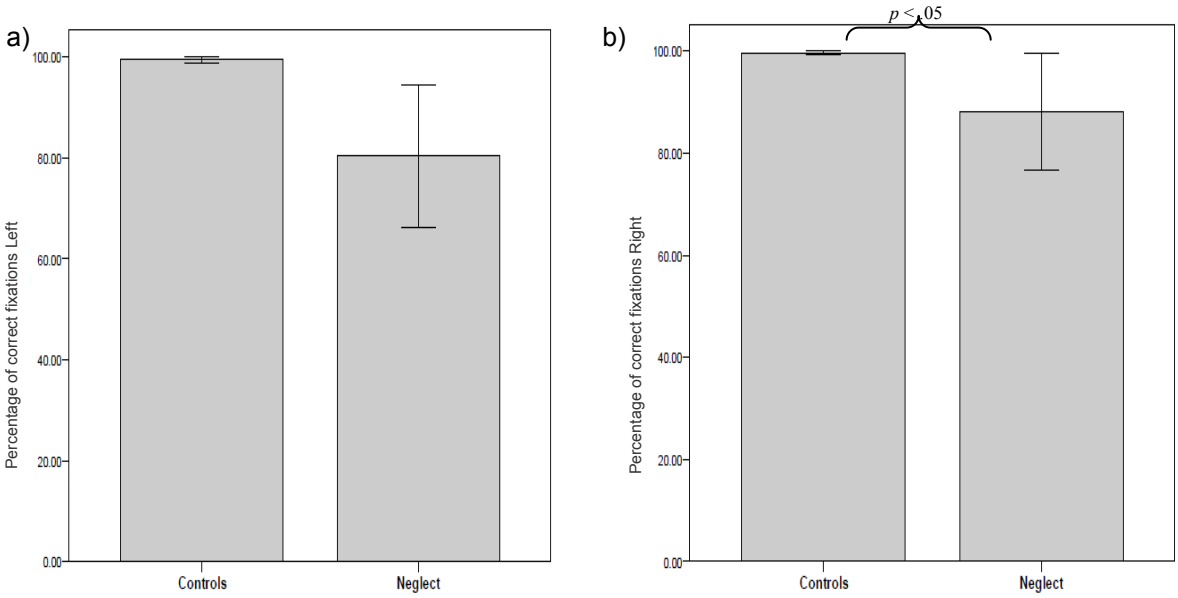


Fig. 2.11: Mean percentage of correct fixations for controls and neglect patients for left (a) and right (b) targets. Error bars show +/- 1 SE.

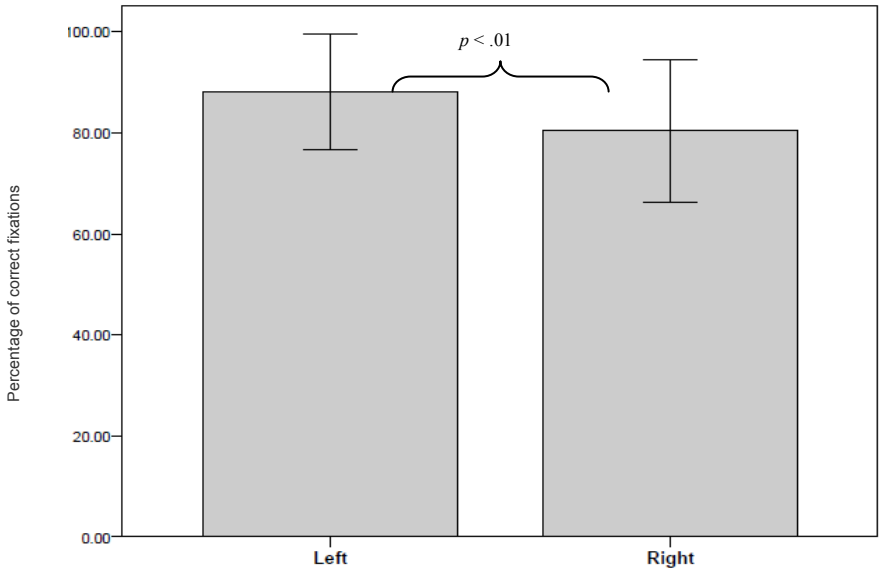


Fig. 2.12: Mean percentage of correct fixations for neglect patients for left and right targets. Error bars show +/- 1 SE; Left vs. Right: $p < .01$.

On an individual level (see also table 2.18) patient JS struggled to maintain fixation on both sides (p<.001 for left and right targets, two-tailed). Patient JM was impaired for right targets (p<.001, two-tailed) while he had no problems to inhibit eye movements towards the left side (p>.05, two-tailed)

Table 2.18: Percentage of correct fixations for left and right targets; group means and individual data for neglect patients.

	correct fixation [%] target left	**correct fixation [%]** target right
Controls	100 (SD 1.1)	99 (SD 2.1)
Neglect	88 (SD 25.1)	80 (SD 31.6)
JS	42	26
JCA	100	100
JQ	98	98
JM	100	77
TH	100	100

Finally, to reveal possible relationships between the fixation and the anti-saccade performance, Spearman's rho correlations were calculated. For the healthy controls there seemed to be no relationship between the ability to respond correctly to left target fixation trials and left target anti-saccade trials (r=-.044, p=.893, N=12). The same applied for right targets (r=-.044, p=.893, N=12). For the neglect patients a negative correlation was found for left targets (r=-.224, p=.718, N=5) and right targets (r=-.308, p=.614, N=5) (fig. 2.13). This is in agreement with the finding that the neglect patients showed a severe bilateral impairment for anti-saccades but were able to withhold saccades much better in the fixation condition. However, the results were not significant, almost certainly due to the small number of data points.

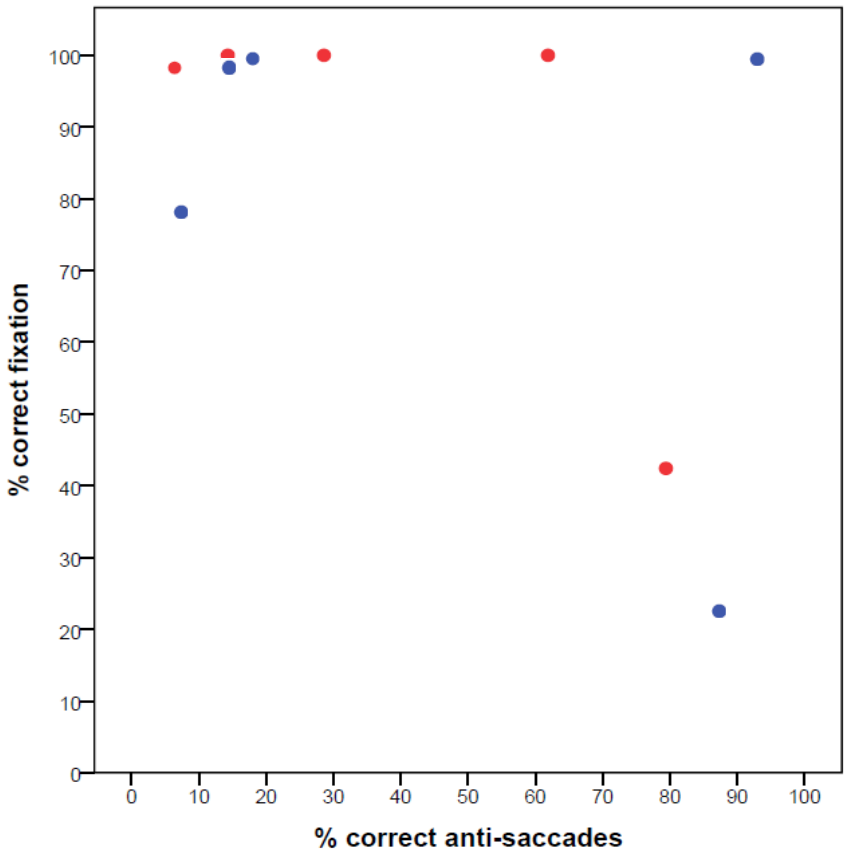


Fig. 2.13: Scatter plot of the correlation between the percentages of correct anti-saccades and correct fixations for left targets (red dots) and right targets (blue dots) for the neglect patients.

2.2.3. Discussion

Pro-saccades

Although many studies report that neglect patients are impaired in responding to contralesional targets (e.g. Duhamel et al., 1992; Niemeier & Karnath, 2003), the neglect patients in the present study did not fail to respond to left targets. Similar results were found by Rossit et al. (2009b), who reported that the neglect patients in their study almost never failed to point to a left target. Furthermore, a previous two-case-study by Harvey et al. (2002) reported that the neglect patients were able to saccade to a left target when it was presented alone. This finding is comparable with the present results. Butler et al. (2009) suggested the possibility that pro-saccades to the left side might be

executed because the patients knew that a stimulus would appear either at the right or the left side of the screen. Thus it can be presumed that the patients made a saccade to the left side, after no target appeared on the right side. This would also explain the longer latencies for the leftward pro-saccades I found. However, Butler et al. (2009) also assumed that on-line performances like pro-saccades are not generally impaired for most neglect patients.

I found overall longer latencies for left targets compared to right targets for neglect patients while no difference between left and right targets was found for the control subjects. Although the mean reaction time towards left targets appeared to be longer for neglect patients compared to the healthy controls, on an individual level no patient showed significantly longer latencies than the controls. Therefore, I assume that my patients indeed saw the targets on both sides and generated saccades towards it as quickly as possible. However, other studies have reported that limits to this simple design quickly become very obvious: as soon as distractors appear along with the target, neglect patients would fail to respond to left targets (Harvey et al., 2002; Olk, Harvey & Gilchrist, 2002).

Regarding the accuracy of the eye movements in my study, almost all neglect patients showed decreased accuracy when saccading towards left targets. Only TH showed no impairment to left targets. However, the patients I tested were also impaired for rightward targets. Again the pro-saccades they executed were inaccurate but not as much as for left targets. Thus I found a clear difference between left and right saccades with a greater accuracy impairment for the left side. The healthy controls showed no difference between left and right targets.

To summarise my findings for the pro-saccade condition, I observed the expected leftward biases with slightly longer latencies and greater inaccuracy for the

neglect patients in my study. These results are in line with previous findings (e.g. Girotti et al., 1983; Niemeier & Karnath, 2003; Butler et al., 2009).

Unfortunately I cannot make any certain predictions about the influence of visual field deficits on the pro-saccades as only three of the five neglect patients were tested for hemianopia. Only one of these three neglect patients showed showed hemianopia. Looking at his data, this patient showed no greater impairment for pro-saccades compared to the other patients. Therefore I presume that the presence or absence of a visual field deficit had no crucial influence. Similar results about the lack of influence of hemianopia on the performance of neglect patients have previously been reported in other studies (e.g. Harvey et al., 2003).

Anti-saccades

As explained above, the neglect patients never failed to execute a correct saccade in the pro-saccade condition, i.e. to saccade towards the target, although the accuracy of the landing point was low. However, damage to the ventral visual stream has repeatedly been reported to cause an inability to execute off-line actions like delayed or pantomime performances (e.g. Goodale, Jakobson & Keillor, 1994; Carey et al., 2006). As Milner and Goodale (1995) speculate that the IPL, an area that is frequently damaged in neglect patients (Mort et al., 2003), receives input from the ventral stream it is very likely that patients who have lesions to these areas are impaired in off-line actions. Furthermore, Rossit et al. (2009a), found a strong involvement of superior temporal lobe areas in off-line actions. Again these structures of are close to the ventral stream (e.g. Milner & Goodale, 1992) and Rossit and colleagues argue that damage to these structures causes difficulties to perform off-line actions.

Indeed, looking at the anti-saccade condition, the neglect patients were clearly impaired on this task compared to the healthy controls. The percentage of correct anti-

saccades was very low with a large number of erroneous pro-saccades generated to both sides. Moreover, in the limited cases where a correct anti-saccade was performed, the accuracy was reduced. The patients clearly failed to find the correct mirrored target location.

Most surprisingly, neglect patients were impaired for right and left targets. Only 38% of the anti-saccades away from left targets and 43% of the saccades away from right targets were generated in the correct direction, and these were observed to have low accuracy. Due to the fact that many of the erroneous pro-saccades were immediately corrected, i.e. a corrective saccade away from the target in the correct direction was executed, it seems reasonable to assume that all participants had understood the task. Similar results were reported by Butler et al. (2009) and also by Rossit and Harvey (2008) who tested neglect patients with an anti-pointing task. In line with the present oculomotor task, Rossit and Harvey found non-lateralized deficits in an anti-pointing task.

In line with Butler and colleagues (2009), I speculate that the failure in the anti-saccade task could either be the inability to perform off-line actions in general, i.e. to perform a vector inversion and remap the target location to the opposite side or instead an inhibition problem.

Interestingly, the neglect patients executed correct anti-saccades as quickly as the healthy controls. So the timing for anti-saccades towards the correct (mirrored) direction appeared to be the same as for healthy controls yet the accuracy of these anti-saccades was low. Therefore it can be assumed that the patients actually saw the peripheral target stimuli (see also discussion for pro-saccades). According to these results it is likely that it did not take them longer to locate the target side but that they had problems to find the correct endpoint location for the anti-saccade.

A closer look at the individual performances and lesions of the neglect patients I tested, revealed that patient JS was very much impaired and executed only a few correct anti-saccaded to both sides. As he has a damage to the temporal lobe his results could support the view that his impairment in performing off-line actions may be caused by a lesion to the ventral stream and related areas. On the other hand, patient TH with his temporal lesion is unimpaired and does not confirm this hypothesis. Furthermore, patient JCA, who has a parietal and occipital lesion, performed very well in the anti-saccade condition with only slightly longer latencies for left targets but an overall perfect performance for right targets. With regard to this result it is very likely, that his impairment for left targets might be a neglect typical failure to detect the correct target position on the left side.

However, beside the vector inversion, participants firstly had to inhibit the reflexive, goal directed response towards the target. Although most studies agree with a frontal lobe involvement in inhibition processes (e.g. Guitton, Buchtel & Douglas, 1985; Meyniel et al., 2005), there is evidence that more posterior brain areas might also be important for inhibition (e.g. Munoz & Wurtz, 1993; Munoz & Istvan, 1998; Johnston & Everling, 2006; Butler et al., 2006). Butler and his colleagues (2006) also reported a patient with a right temporo-parietal lesion who was unable to inhibit task irrelevant distractors. Indeed, evidence for an inhibition problem could come from the observation that the erroneous pro-saccades during the anti-saccade condition showed similar SRTs to the SRTs in the pro-saccade condition, which is supposed to be reflexive and stimulus driven (e.g. Everling & Fischer, 1998). Therefore it might be possible that the patients in my anti-saccade task were unable to withhold their reflexive eye movements towards the target rather than displaying a problem with the vector inversion.

By looking at the anti-saccade performance only, I cannot make any further predictions about the reason for the bilateral errors of the neglect patients. Like Butler et al. (2009), I can only suggest at this point that the failure could either be an inability to inhibit reflexive eye movements towards the target or problems to remap the target location to the opposite side. The additional fixation task was therefore conducted to narrow the possible reasons for the anti-saccade deficit allowing an assessment of the neglect patient's ability to inhibit stimulus driven saccades.

Fixation

Unlike the anti-saccade data, the results of the fixation condition showed a significant difference between trials in which the target appeared to the right and the left side. For left targets, the group analyses revealed no impairment. Four of five neglect patients could inhibit reflexive eye movements as well as the healthy controls. It could be argued, that neglect patients tended to ignore the left side and therefore had no difficulties in inhibiting the saccades as they did not see the target at all. Previous studies by Duhamel et al. (1992) and Niemeier and Karnath (2003) for example have found that neglect patients are impaired in their responses to left targets. But as described above, the neglect patients in my study responded towards left targets when it was required in the pro-saccade condition. Likewise, Harvey et al. (2002) and Rossit et al. (2009b) have reported that neglect patients were able to look and point towards left targets when they were presented alone. Moreover, the numerous erroneous pro-saccades of patient JS in the fixation trials show that he saw the target. Thus, it can be assumed that the patients in my study did in fact have to inhibit the eye movement in this fixation condition to perform the task correctly.

For right sided targets, two of the five patients (JS and JM) showed the expected neglect typical right-sided bias as they clearly had problems to inhibit the eye

movement towards the target and made many erroneous pro-saccades instead of maintaining fixation on the central dot. As the saccade inhibition is only impaired in two of the patients, it can be assumed that the fixation deficit is caused by the typical oculomotor behaviour shown in neglect patients rather than by a general inhibition deficit. All other three patients were able to inhibit stimulus driven saccades towards right targets perfectly. Moreover, patient JM, who was impaired to maintain fixation for right targets, showed no difficulties to inhibit saccades towards left targets. This result is not surprising as strong ipsilesional biases in the spatial modulation of neglect patients have been reported in other studies (e.g. Niemeier & Karnath, 2003).

Inhibition deficits are usually related to dysfunctions in the frontal lobe and various studies found evidence that they result in a bilateral or contralesional inability to inhibit eye movements (e.g. Barton et al., 2008; Machado & Rafal, 2004). Only one of the five neglect patients that were tested had a lesion involving the frontal lobe. However, he showed only a neglect typical impairment for the right side and never failed to inhibit a leftward target.

In general, the correlation between correct anti-saccades and correct fixation trials showed a negative (if non-significant) relationship with most neglect patients performing very well for fixation trials but being impaired for anti-saccades.

Conclusion and rationale for experiment 2

The pro- and anti-saccade tasks of this current study were adopted from Butler et al. (2009) and the main outcome presented here is in agreement with Butler's results. In both studies, the neglect patients made many erroneous pro-saccades to right and left targets. Importantly though, an additional fixation task was conducted to take a closer look at the underlying reasons for these bilateral errors and to approach the question if

the failure is based on insufficient inhibition of the stimulus driven saccade or a faulty remapping of the target location to the opposite side.

In the fixation task, only one of the neglect patients (JS) was severely impaired bilaterally in inhibiting eye movements instead of maintaining fixation. Another neglect patient (JM) showed a typical rightward lateral bias but was able to inhibit leftward saccades perfectly. The other three patients performed flawlessly with almost 100% correct fixations in left and right target trials. From these results I conclude that no general inhibit impairment could be found.

Only patient JS was impaired bilaterally in the anti-saccade as well as the fixation condition. Thus, his overall results show that inhibition deficits might have contributed to the anti-saccade impairment instead of the erroneous pro-saccades being a remapping problem only.

Patients JQ and JM also showed severe bilateral anti-saccade errors but, apart from JM's neglect typical impairment to occasionally execute saccades towards right targets in the fixation condition, both showed no general problems to withhold eye movements when it was required. From these results I conclude, that their anti-saccade deficits can be seen as a vector inversion problem rather than an inhibition impairment.

Although my data support the idea that bilateral anti-saccade failures in neglect patients might be caused by a problem to execute off-line actions, it has to be kept in mind that only five patients were tested with the additional task and one patient (JS) did not conform. Furthermore, from these five patients only three were severely impaired for left and right targets in the anti-saccade task. Moreover, as I used blocked conditions, i.e. my fixation condition did not contain any other trials than fixation trials, the patients knew for every trial what they had to do a priori. Thus I cannot state that neglect patients do not show inhibition failures as my fixation task was very simple. Therefore, for experiment 2, I used a more complex task interleaving pro-saccades and

fixation trials to investigate the inhibition ability of stroke patients in greater detail. As only two of my patients for the current, simple fixation experiment had a lesion that would allow me to make predictions about the dorsal and ventral stream model, more patients need to be tested. In the following experiment, that will take a closer look at the inhibition ability, I recruited a larger number of stroke patients.

2.3. Experiment 2: Interleaved pro-saccade and fixation trials

As the first experiment was very simple with no variations within the blocks, i.e. 100% pro-saccades, 100% anti-saccades and 100% fixation trials, a second inhibition task that interleaves pro-saccades and fixation trials will be conducted..

Olk and Kingstone (2009) have previously found that the variations of the percentage of fixation or anti-saccade trials that are interleaved with pro-saccade trials in the same block have an impact on reaction time and accuracy. In their experiment, the interleaved conditions consisted of 10% fixation or anti-saccade trials with 90% pro-saccade trials, 30% fixation or anti-saccade trials with 70% pro-saccades and 50% fixation or anti-saccade trials with 50%. Additional blocks with 100% fixation trials, 100% anti-saccade trials and 100% pro-saccade trials were also ran. As I will use fixation and pro-saccade trials in my second experiment only, I will just focus on these results from Olk and Kingstone's study.

Olk and Kingstone found longer latencies for pro-saccades in conditions that had a high amount of interleaved fixation trials (e.g. 50% pro-saccades and 50% fixation trials) compared to blocks in which the majority of the trials were pro-saccades (e.g. 90% pro-saccades and 10% fixation trials). Likewise, in conditions with a majority of pro-saccade trials, more erroneous pro-saccades were found for fixation trials compared to conditions that consisted of a higher percentage of fixation trials. Therefore this follow-on experiment to the first simple experiment will be conducted to take a closer look at inhibition by using Olk and Kingstone's (2009) paradigm instead of a simple 100% fixation task.

If the patients again show no failure to inhibit reflexive saccades in fixation trials here, this would support a view whereby bilateral anti-saccade failures can be argued to be a remapping (off-line action) problem rather than an inhibition problem.

2.3.1. Method

Healthy participants

14 healthy elderly right-handed subjects (mean age 71.1 years, SD 5.6) participated in the study and were reimbursed for travel expenses. All subjects consented in writing to taking part in the experiment.

Patients

Twelve right hemisphere stroke patients took part in the study. All patients were assessed with the *BIT* (Wilson, Cockburn & Halligan, 1987) and with the *Line Bisection Test* (Harvey, Milner & Roberts, 1995) and the *Balloons Test* (Edgeworth, Robertson & McMillan, 1998) to identify hemispatial neglect.

Seven of my patients were identified with hemispatial neglect (mean age 63.4 years, SD 8.4). Three of the neglect patients (PI, AB, AK) were impaired in all three neglect tests, neglect patient JK showed a rightward bias in the line bisection and the balloons test, patient JH scored clearly below the cut-off in the line bisection task and patient JMV showed an impairment for left targets in the balloons test. Only patient MM never showed impairment in any neglect tests but as family members and therapist/clinical staff reported neglect typical behaviour (for example bumping into things on the left side) she was included in the neglect group as well.

In four cases more than two years had elapsed between the assessments and participation in the current experimental task, therefore these patients (MM, JK, JH, AK) were re-tested with the BIT. All attained scores above the cut-off in the second assessment indicating that they had recovered. However, as they were previously identified with neglect and as they could possibly still be impaired in the other tests they

were included in the neglect group (N+) with the acute neglect patients PI, AB and JMV.

Another five right hemisphere stroke patients who had never suffered from neglect (mean age 59.8 years, SD 10.9) took part in the study as well. Although patient DR scored slightly below the cut-off for neglect in the balloons test he was added to the no-neglect group (N- group) as he performed almost perfectly in the BIT and even showed a leftward bias in the line bisection task.

All patients were also tested for visual field deficits. Seven of my twelve patients showed hemianopia for the left visual field and one patient (JS) showed a lower left quadrantanopia. Another laptop based test was used to examine visual extinction. In this test the participant had to detect a black square at the left, the right or on both sides of a central fixation dot. The test consisted of 70 trials with 20 single left targets, 20 single right targets, 20 trials in which left and right targets were presented simultaneously and 10 trials in which no target appeared at all. Half of the targets were presented at 2.2 degrees away from the central fixation dot and the other half at 4.4 degrees. Four patients (PI, JH, AK, JMV) failed to respond to left targets when these were simultaneously presented with another target on the right side, thus showing extinction. However, as patient PI also did not respond to single targets on the left side it cannot be said for sure if his failure to detect the left box when a right one was presented at the same time was the result of extinction or of his serious neglect. He never missed a square on the right side.

As the experimental task involves a quick change of response pattern within the same block of trials, patients were assessed with the subtest *Rule Shift Cards* of the Behavioural Assessment of the Dysexecutive Syndrome (BADS, Wilson et al., 1996) which tests cognitive flexibility and detects preservative tendencies. The test consists of 21 red and black playing cards and requires a different response to the same target in the

second of two immediately successive trials. The test score takes speed and correctness of answers into account. I was able to test ten of my twelve stroke patients with the BADS and the majority of them performed perfectly, with four patients receiving the maximum possible score of four and another six patients receiving a score of three. Only two patients were impaired in responding correctly and fast enough during the second block of trials when the instruction had changed compared to the first block of trials. Patient AK received a score of two and patient DR received a score of zero with numerous errors and long reaction times, showing difficulties in inhibiting the previously required responses. Please see table 2.19 (a) and (b) for demographic and clinical details and figure 2.14 for lesion locations.

Patients were recruited from the Southern General Hospital in Glasgow. The study was conducted in accordance with the ethical guidelines of the South Glasgow University Hospitals NHS Trust and the Declaration of Helsinki. All participants gave their informed consent prior to the study.

Table 2.19 (a): Demographic and clinical data of right hemisphere stroke patients.

PATIENT	GENDER	AGE	SCAN	ETIOLOGY	LESION LOCATION	VISUAL FIELD DEFICIT	EXTINCTION
PI	M	56	MRI	Infarct	fronto-temporo-parietal	YES	YES
AB	F	72	MRI	Infarct	temporo-occipital	YES	NO
MM	F	66	MRI	Infarct	dorsal frontal, parietal, corona radiata	NO	NO
JK	F	72	CT	Infarct	fronto-temporal	NO	NO
JH	F	58	MRI	Infarct	fronto-temporo-parietal	YES	YES
AK	F	69	CT	Infarct	posterior frontal, posterior insular, parietal	NO	NO
JMV	M	51	CT	Infarct	Right MCA, fronto-temporo-parietal	YES	YES
DR	M	75	CT	Haemorrhage	Basal ganglia, internal capsule, thalamus	YES	NO
WG	M	67	MRI	Infarct	Right MCA, basil ganglia and pallidus, frontal + temporal cortex	YES	NO
JS	M	56	CT	Infarct	dorsal frontal, posterior temporal, parietal	YES	NO
RI	M	49	MRI	Infarct	Right MCA, frontal, insular, temporal, parietal	NO	NO
AMI	F	52	CT	Infarct	Lentiform nucleus, head of caudate, temporal	NO	NO

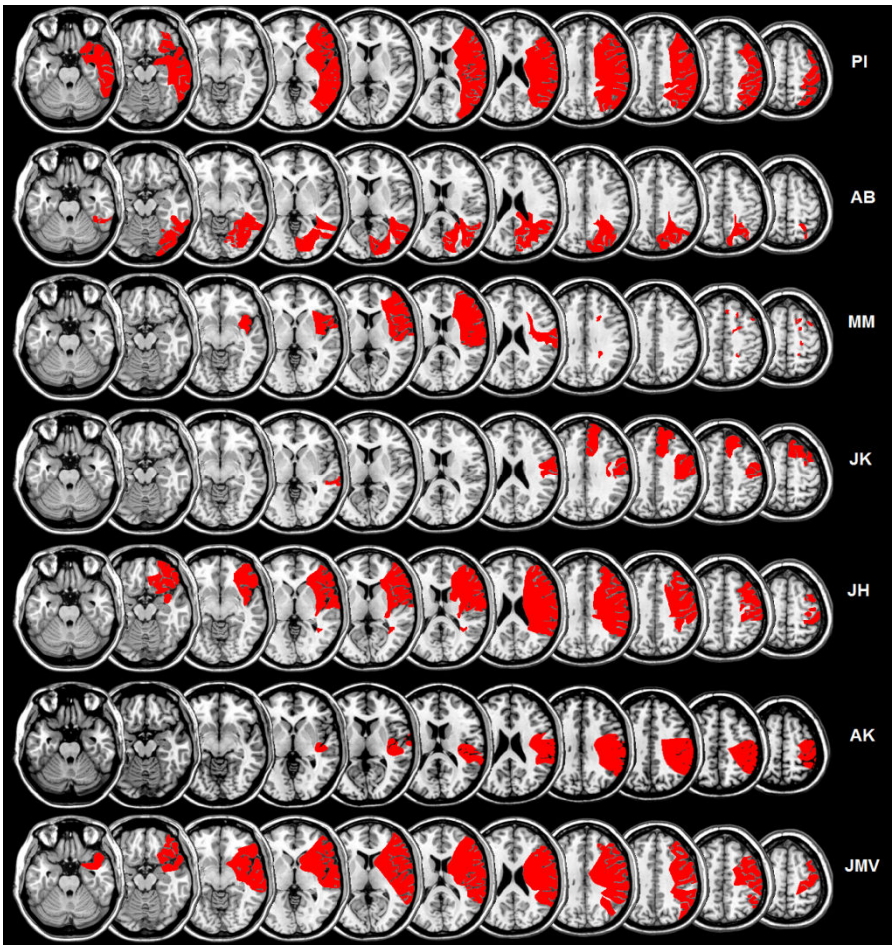
Table 2.19 (b): Clinical data of right hemisphere stroke patients.

PATIENT	TIME SINCE INJURY ONSET 1	LINE BISECTION	BALLOONS	BIT 1	TIME SINCE INJURY ONSET 2	BIT 2	BADS	GROUP
PI	5	50	11%	84	-	-	3	N+
AB	11	12	0%	129	-	-	-	N+
MM	2	3	59%	142	31	144	4	N+
JK	4	15	44%	141	38	135	3	N+
JH	10	14	50%	132	43	139	4	N+
AK	1	16	43%	121	25	142	2	N+
JMV	9	5.6	23%	140	-	-	-	N+
DR	5	-3.3	44%	143	-	-	0	N-
WG	3	5.6	50%	143	-	-	3	N-
JS	14	1	53%	146	-	-	4	N-
RI	3	3	50%	146	-	-	4	N-
AMI	3	4.8	47%	138	-	-	3	N-

BIT = Behavioural Inattention Test (cut-off score 129), Line Bisection cut-off score 6; Balloons cut-off score 45%, BADS = Behavioural Assessment of the Dysexecutive Syndrome (max test score 4).Time Since Injury Onset 1 = time (in months) elapsed when assessed for the first time, but if time between assessment and participating in experiment was too long, patients were retested with the BIT (BIT2), Time Since Injury Onset 2 = time (in months) elapsed when retested; N+ = neglect group, N- = no neglect group

Lesion locations

(a)



(b)

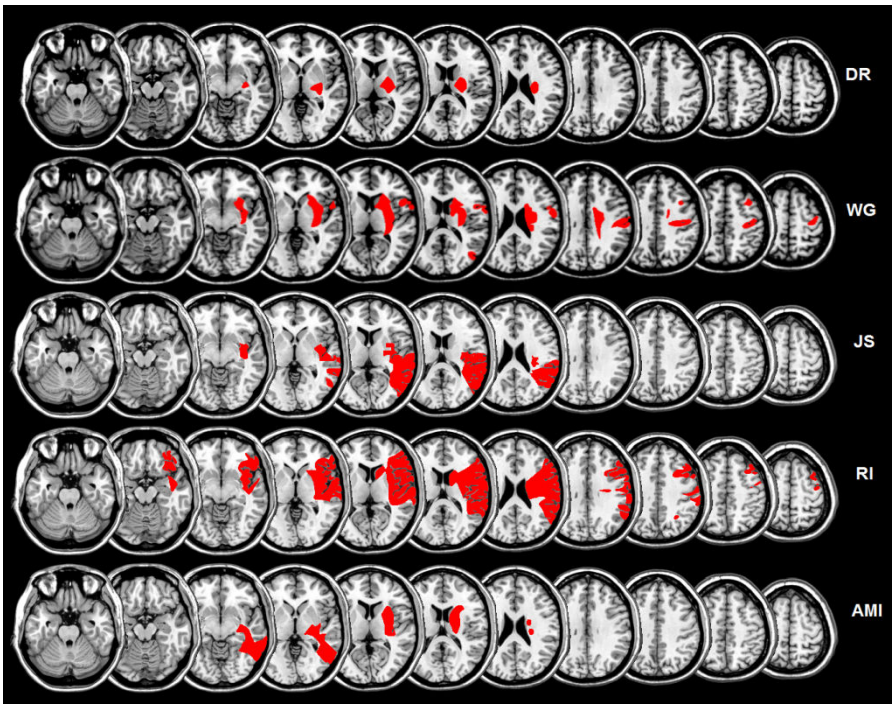


Fig. 2.14: Voxel-based lesion map for each patient with hemispatial neglect (a) and without hemispatial neglect (b) in axial view.

Apparatus and stimuli

A black circle with a diameter of 0.6 degrees was displayed in the centre of the computer screen and served as a fixation point. A green dot (same size and location) served as a go signal in pro-saccade trials and a similar red dot indicated a stop trial. Target stimuli consisted of black circles (similar to the fixation point), which were presented on a horizontal axis either 7.3 degrees to the left or the right side of the central circle.

Targets were presented on a 17" SVGA monitor with 800 x 600 pixel resolution and 74 Hz refresh rate. The monitor was located at 57 cm from the chinrest. A second PC was used to record eye position data on-line. Eye movements were monitored with the SMI EyeLink System (SensoMotoric Instruments GmbH, Teltow, Germany). The system uses the centre of the pupil and the corneal reflection technique to define pupil position. Eye movements were recorded at 250 Hz, with an operational spatial resolution of about 0.3 degrees. Saccade onset was defined as a change in eye position with a minimum velocity of 35º/s or a minimum acceleration of 9,500º/s2. Targets presentation was controlled by SR Research Experiment Builder software version number 1.4.624.

Procedure

At the beginning of each session the instructions for the oculomotor task were presented in written form. Additionally the instructions were verbally explained and a few pro-saccade and fixation trials were demonstrated until the participant had understood the task.

The experimental task consisted of five blocks with interleaved pro-saccade and fixation trials. The blocks differed in the percentage of saccade and fixation trials and each participant completed all five blocks. Block 1 consisted of 0% fixation trials and

100% pro-saccade trials. The percentage of pro-saccade trials decreased in block 2, 3 and 4 with 90%, 70% and 50% pro-saccade trials and 10%, 30% and 50 % fixation trials respectively. Block 5 contained 100% fixation trials. 40 trials were presented in block 1 and 5, while block 2, 3 and 4 consisted of 80 trials. The sequence of fixation and pro-saccade trials were randomised in each block and an equal number of left and right targets were presented in random order within each block. Furthermore, the block sequence was counterbalanced.

Each of the five blocks started with a nine-point grid calibration and validation procedure (for details please see chapter 2.2). For the experimental task, participants had to fixate the central dot with their eyes steady on this fixation point. This was monitored on the second computer screen. Then the actual task was manually started immediately and the central dot changed colour to red or to green. At the same time a target appeared at the left or the right side of the central dot for 2,000 ms while the fixation point remained visible. With a green fixation dot, a pro-saccade towards the peripheral target was required, whilst a red dot indicated that the participant had to maintain fixation on the centre dot. Each trial ended with the disappearance of both dots and the screen went blank for another 1,000 ms until a new fixation point appeared. Example displays are shown in figure 2.15.

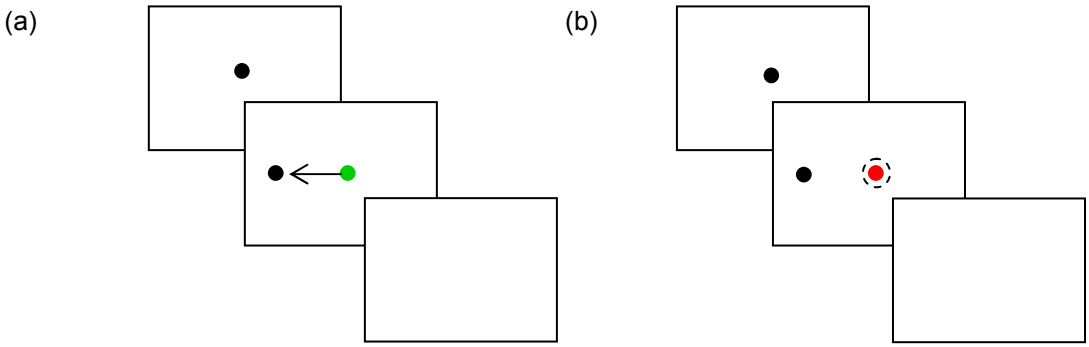


Fig. 2.15: Schematic layout of the pro-saccade and fixation trials. Pro-saccade trials (a) were indicated by a green central circle and the participant had to initiate a saccade towards the peripheral target circle which appeared for 2,000 ms as quickly and as accurately as possible. In the fixation trials (b) a red centre circle indicated that the participant had to maintain fixation on the central dot while a peripheral target was presented for 2,000 ms on the left or right side.

Data processing

A pro-saccade was identified as correct when the participant made a saccade bigger than 2 degrees towards the target. Likewise, a fixation was correct when no saccade bigger than 2 degrees along the horizontal axis occurred. Trials in which participants made a saccade with a latency shorter than 80 ms were considered anticipatory and excluded from further analysis. Also, trials in which the central circle was not properly fixated (deviation larger than 1 degree) were excluded from analyses. Finally, pro-saccade trials with saccades bigger than 12 degrees were also excluded as I found that some of the saccades went far beyond the target. On the other hand and contrary to the anti-saccade study in chapter 2.2, I kept saccades with amplitudes shorter than 1 degree as a great amount of the neglect patients' pro-saccades in this study were either very short or not executed, possibly as a result of neglect. Keeping the short eye-movements to be a correct pro-saccade and thus categorising them later as errors, allowed a realistic view of the saccadic performance and would reveal a possible neglect typical omission for left targets.

These criteria resulted in an exclusion of 7.1%, 12.7% and 12.8% of all pro-saccade trials across condition 1-4 for the controls, neglect patients (N+) and no-neglect patients (N-) respectively. For fixation trials I rejected an average of 3.3%, 4.5% and 4.1% across condition 2-5 for controls, N+ group and N- group respectively. Detailed information for each exclusion category can be found in table 2.20.

Table 2.20: Percentage of excluded trials for the anticipation, fixation and amplitude criteria, for pro-saccades (condition 1, 2, 3 and 4) and fixation trials (condition 2, 3, 4 and 5) and presented separately for controls, neglect patients and no-neglect patients.

		Pro-saccades				Fixation			
		C1	C2	C3	C4	C2	C3	C4	C5
Controls	**anticipation**	2.3%	3.6%	2.4%	2.9%	0.5%	1.2%	1.8%	3.6%
	fixation	1.8%	4.8%	3.8%	2.4%	0.4%	1.5%	2.6%	1.7%
	amplitude	0.2%	1.4%	2.4%	0.9%	-	-	-	-
Neglect	**anticipation**	7.2%	15.5%	8.7%	6.7%	0.7%	4.3%	5.5%	5.5%
	fixation	2.3%	4.8%	1.3%	1.5%	0.7%	0.2%	0.5%	0.7%
	amplitude	1.3%	0.3%	1.3%	-	-	-	-	0.2%
No Neglect	**anticipation**	7.2%	12%	8%	8%	1.3%	2.8%	4%	3,5%
	fixation	2.3%	6.2%	1.7%	3%	1.7%	0.5%	1.7%	2.7%
	amplitude	1.3%	0.8%	0.3%	0.3%	-	-	-	0.3%

2.3.2. Results

Analyses were conducted separately for pro-saccade and fixation trials. Only the first saccade after stimulus onset was used. For the statistical analyses, repeated measures ANOVA and post-hoc pairwise comparisons with Bonferroni adjustment ($p<.05$) were carried out. Crawford and Howell's modified t-test (1998) was used to compare individual data with the control group for some of the variables.

2.3.2.1. Pro-saccades

For pro-saccade trials I analysed conditions 1, 2, 3 and 4 and the *percentage of correct saccades*, the *absolute angular error* and the *SRT* were calculated. These variables were previously described in chapter 2.2.2.

The control participants performed very well with 96% (conditions 1, 2 & 3) and 94% (condition 4) of *correct pro-saccades* for left targets and 97%, 95%, 93% and 97% (conditions 1, 2, 3 and 4) for right targets. While N+ patients showed a clear impairment for left targets with 64%, 63%, 65% and 59% correct pro-saccades towards left targets, they reached a higher percentage of correct responses for right targets with 97%, 85%, 86%, 82% for condition 1, 2, 3 and 4. Finally, N- patients showed 88%, 69%, 82% and 67% correct responses for left targets and 97%, 87%, 89% and 85% for right targets in conditions 1 to 4 (see also table 2.22).

For the dependent variable percentage of correct pro-saccades, a 3x2x4 mixed ANOVA with *group* as a between-subject factor and *side* of target and *condition* as the within-subject factor revealed main effects of *group* [$F_{(2,23)} = 4.4$, $p<.05$], *side* [$F_{(1,23)} = 9.8$, $p<.01$] and *condition* [$F_{(2.23,51.29)} = 8.1$, $p<.001$]. This was qualified by significant *side x group* [$F_{(2,23)} = 4.3$, $p<.05$] and a *condition x group* [$F_{(4.46,51.285)} = 4.3$, $p<.05$] interactions (table 2.21). As Mauchly's test of Sphericity revealed that the assumption of sphericity had not been met for *condition* (Mauchly's W=.565; $p<.05$), the Greenhouse-Geisser correction was used.

Table 2.21: ANOVA with the factors side, condition and group for correct pro-saccades. Significant main effects and/or interactions in italic; * = Greenhouse-Geisser correction for df.

		df	F	Sig.
Within-Subjects Effect	***Condition***	*2.23**	*8.112*	*< .001*
	Condition x Group	*4.46**	*2.504*	*.048*
	Error (Condition)	51.285*		
	Side	*1*	*9.772*	*.005*
	Side x Group	*2*	*4.323*	*.025*
	Error (Side)	23		
	Condition x Side	3	2.109	.107
	Condition x Side x Group	6	1.635	.151
	Error (Condition x Side)	69		
Between-Subjects Effect	**Group**	2	3.844	.069
	Error	23		

A closer look at the *group by side* interaction with pairwise comparisons revealed that the neglect patients performed significantly worse than the healthy controls for left targets only ($p<.05$). Also, only the neglect group executed fewer correct pro-saccades towards left targets compared to right targets ($p<.01$) (fig. 2.16). No other comparisons proved significant.

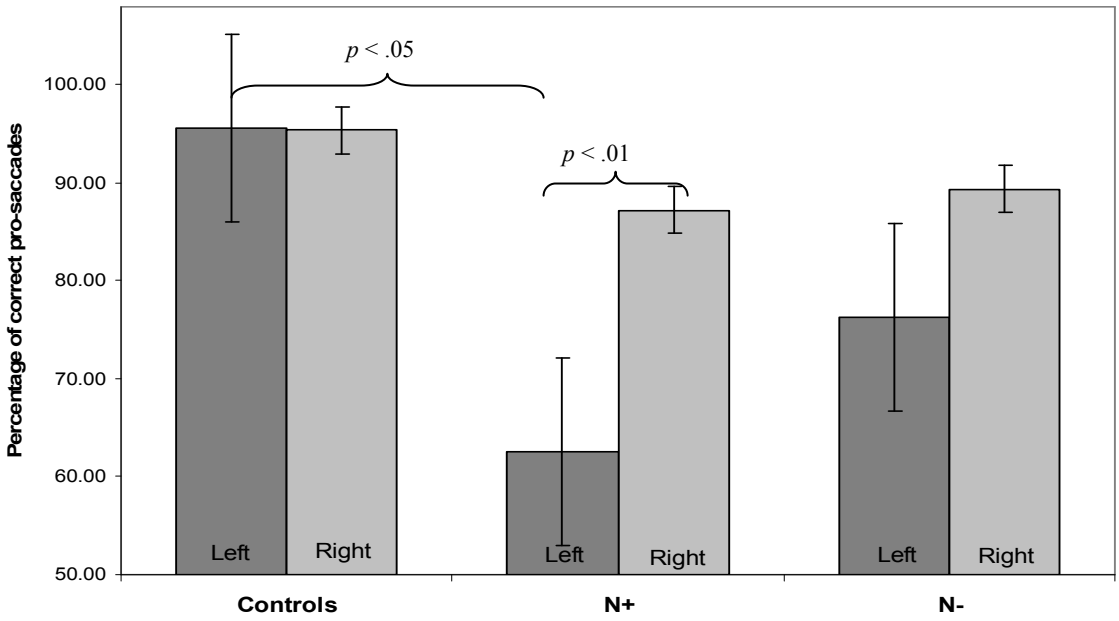


Fig. 2.16: Percentage of correct pro-saccades; means for the healthy controls, N+ and N-group for left and right targets. Error bars show +/- 1 SE;

Regarding the *condition x group* interaction, the results were very irregular. Pairwise comparisons revealed, that the N+ group performed significantly worse than the healthy controls for conditions 2 (mean difference 21.9% [$p<.05$]) and 4 (mean difference 25.2% [$p<.05$]). No difference was found for conditions 1 and 3. Further comparisons between the groups also revealed, that the no-neglect patients did not differ from any other groups.

Looking at the groups, the no-neglect patients seemed to be irregularly influenced by the different proportions of pro-saccade and fixation trials in the four conditions. Compared to the 100%-pro-saccade-condition (condition 1) they performed significantly worse in conditions 2 (mean difference 14.7% [$p<.01$]) and 4 (mean difference 16.7% [$p<.05$]). No other difference between conditions was found for the N- group.

While the neglect patients showed an overall poor performance with a great number of omitted pro-saccades in most of the conditions, the control participants showed a constant good performance for all conditions. No difference between any conditions was found neither for the control nor the N+ group (fig. 2.17).

On an individual level, N+ patients PI and AB responded to almost none of the left targets. Both responded to right targets but were nevertheless also impaired here compared to the healthy controls. Furthermore, neglect patient JMV was impaired for left targets but for right targets he only showed deficits for the forth condition, which consisted of interleaved 50% pro-saccades and 50% fixation trials. Regarding the N- patients, DR and WG also failed to respond to most of the left targets and also slightly for right targets. For the all individual and group data please see table 2.22.

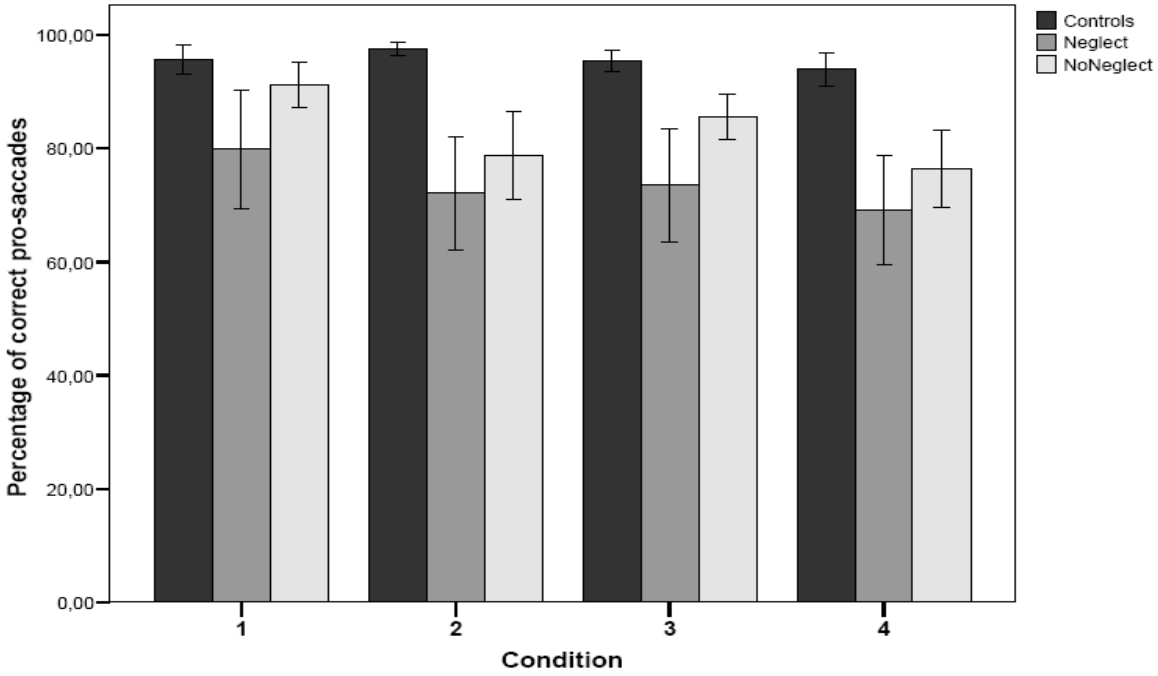


Fig. 2.17: Percentage of correct pro-saccades; means for the healthy controls, N+ and N-group for condition 1, 2, 3 and 4. Error bars show +/- 1 SE;

Table 2.22: Percentage of correct pro-saccades for left and right targets for condition 1 (100% pro-saccades), condition 2 (90% pro-saccades), condition 3 (70% pro-saccades) and condition 4 (50% pro-saccades); group means and individual data.
Significance level for Crawford & Howell's modified t-test (two-tailed): ***=p<.001, **=p<.01, *=p<.05.

			Condition 1	Condition 2	Condition 3	Condition 4
Controls		LEFT	96 (SD 8.2)	96 (SD 6.2)	96 (SD 6.2)	94 (SD 9.7)
		RIGHT	97 (SD 7.5)	95 (SD 6.6)	93 (SD 8.6)	97 (SD 4.7)
N+		LEFT	64 (SD 43)	63 (SD 43.2)	65 (SD 43.2)	59 (SD 43)
		RIGHT	97 (SD 6.3)	85 (SD 13.4)	86 (SD 16.8)	82 (SD 12.9)
N-		LEFT	88 (SD 17.4)	69 (SD 38)	82 (SD 17.2)	67 (SD 30.1)
		RIGHT	97 (SD 6.4)	87 (SD 14.8)	89 (SD 10)	85 (SD 17.8)
N+	**PI**	LEFT	0***	0***	5***	0***
		RIGHT	100	66***	63**	63***
	AB	LEFT	6***	3***	0***	0***
		RIGHT	83	73**	60**	73***
	MM	LEFT	89	100	96	86
		RIGHT	100	82	95	94
	JK	LEFT	93	89	86	100
		RIGHT	100	100	95	76***
	JH	LEFT	93	79*	95	61**
		RIGHT	100	80	90	73***
	AK	LEFT	100	100	97	100
		RIGHT	95	94	96	94
	JMV	LEFT	69**	68***	73**	100
		RIGHT	100	100	100	64***
N-	**DR**	LEFT	63**	38***	55***	56**
		RIGHT	86	63***	75	67***
	WG	LEFT	77*	17***	73**	22***
		RIGHT	100	82	96	64***
	JS	LEFT	100	94	96	88
		RIGHT	100	97	96	92
	RI	LEFT	100	100	94	100
		RIGHT	100	96	81	100
	AMI	LEFT	100	94	91	69*
		RIGHT	100	97	96	100

Looking at the *absolute angular error*, the healthy control participants saccaded very accurately to the peripheral targets with an error of .78, .88, .80 and 1.13 degrees for left and .75, .94, .85 and .91 degrees for right targets. Similar results were found for the N- group with .95, 1.37, .94 and 1.20 degrees for left targets and .84, .72, .72 and .88 degrees for right targets. While the N+ group had no problem in making accurate

eye movements to right targets (.71, .83, .40 and .72 degrees) they showed an impairment for left targets (1.82, 1.99, 1.87 and 1.98 degrees) (see also table 2.24 for all group data). A look at the landing point of the first saccade in relation to the target revealed that most of the eye movements fell too short. As neglect patients AB and PI did not respond to most of the left targets and thus most of their data was missing for the absolute angular error, their performances were not included in the ANOVA.

A 3x2x4 mixed ANOVA for the dependent variable Absolute Angular Error with *group* as a between-subject factor and *side* of target and *condition* as the within-subject factor revealed a main effect for *side* [$F_{(1,21)} = 16.4$, $p<.001$] and a significant *side x group* interaction [$F_{(2,21)} = 8.2$, $p<.01$] (table 2.23). As the assumption of sphericity had not been met for the independent variable condition (Mauchly's W = .239; $p<.001$), the Greenhouse-Geisser correction was used.

Table 2.23: ANOVA with the factors side, condition and group for the absolute angular error for correct pro-saccades. Significant main effects and/or interactions in italic; * = Greenhouse-Geisser correction for df.

		df	F	Sig.
Within-Subjects Effect	**Condition**	1.558*	3.061	< .072
	Condition x Group	3.116*	.317	< .821
	Error (Condition)	32.723*		
	Side	*1*	*16.382*	*<.001*
	Side x Group	*2*	*8.221*	*<.002*
	Error (Side)	21		
	Condition x Side	3	.502	<.682
	Condition x Side x Group	6	1.089	<.379
	Error (Condition x Side)	63		
Between-Subjects Effect	**Group**	2	1.642	< .217
	Error	23		

Pairwise comparisons revealed that neglect patients showed greater inaccuracy when they saccaded towards left targets compared to the healthy controls (p<.05). Moreover, only the neglect group were less accurate for left compared to right targets (p<.001). No other effects were found (fig. 2.18).

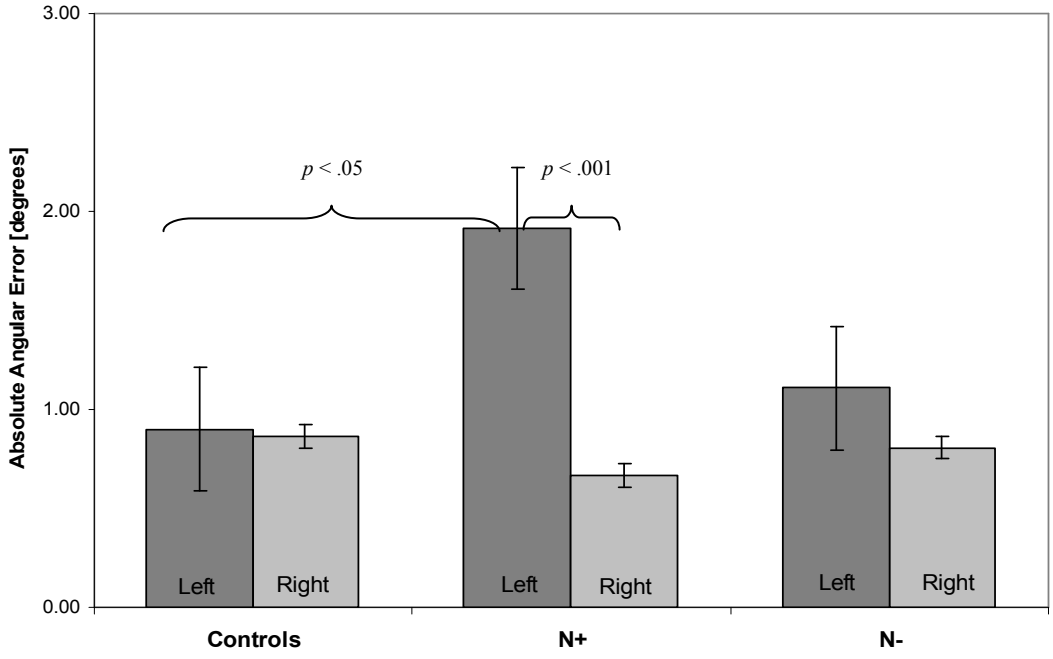


Fig. 2.18: Absolute Angular Error in degrees of correct pro-saccades; means for healthy controls, N+ and N- group for left and right targets. Error bars show +/- 1 SE.

On an individual level, N+ patients PI and AB were severely impaired, particularly in responding to left targets. While they neglected most of the left targets, a modified t-test (Crawford & Howell, 1998) revealed that the few saccades they executed leftwardly were very inaccurate compared to the healthy controls. Also neglect patients MM, JH and JMV showed an overall very low accuracy for left targets. From the N- group only patient DR showed an impairment to execute accurate saccades towards left targets. On the other hand, most patients performed very accurately for right targets. Here only N- patient DR showed a slight impairment for one condition.

For all individual and group data and the results of Crawford and Howell's modified t-test, please see table 2.24.

Table 2.24: Absolute Angular Error in degrees of correct pro-saccades for left and right targets for condition 1 (100% pro-saccades), condition 2 (90% pro-saccades), condition 3 (70% pro-saccades) and condition 4 (50% pro-saccades); group means and individual data.
Significance level for Crawford & Howell's modified t-test (two-tailed): ***=p<.001, **=p<.01, *=p<.05.

			Condition 1	Condition 2	Condition 3	Condition 4
Controls		LEFT	.78 (SD .3)	.88 (SD .4)	.8 (SD .3)	1.14 (SD .9)
		RIGHT	.75 (SD .4)	.94 (SD .4)	.85 (SD .4)	.91 (SD .4)
N+		LEFT	1.82 (SD 1.2)	1.99 (SD 1.5)	1.87 (SD 1)	1.98 (SD 1.2)
		RIGHT	.71 (SD .2)	.83 (SD .3)	.4 (SD .5)	.72 (SD .6)
N-		LEFT	.95 (SD .6)	1.34 (SD .8)	.94 (SD .6)	1.2 (SD 1)
		RIGHT	.84 (SD .7)	.72 (SD .3)	.73 (SD .4)	.94 (SD .4)
N+	**PI**	LEFT	-	-	5.4***	-
		RIGHT	0.58	0.72	0.95	1.53
	AB	LEFT	4.65***	5.18***	-	-
		RIGHT	0.38	0.77	1.4	1.13
	MM	LEFT	1.91**	2.05**	2.04**	2
		RIGHT	0.65	0.47	0.7	0.54
	JK	LEFT	0.96	1.31	1.71*	0.88
		RIGHT	0.52	0.98	0.44	0.62
	JH	LEFT	2.03**	1.8*	1.91**	2.54
		RIGHT	0.67	0.65	0.58	0.27
	AK	LEFT	0.55	0.35	0.48	0.76
		RIGHT	0.76	1.25	0.49	0.47
	JMV	LEFT	3.65***	4.44***	3.18***	3.71*
		RIGHT	0.92	0.77	0.77	1.69
N-	**DR**	LEFT	1.82**	2.69***	1.8**	1.94
		RIGHT	1.84*	0.74	1.36	1.36
	WG	LEFT	1.29	1.51	1.21	2.51
		RIGHT	0.56	1.22	0.62	0.84
	JS	LEFT	0.65	1.12	0.71	0.83
		RIGHT	1.1	0.5	0.68	1.08
	RI	LEFT	0.47	0.76	0.47	0.37
		RIGHT	0.45	0.54	0.29	1.05
	AMI	LEFT	0.49	0.76	0.49	0.33
		RIGHT	0.23	0.61	0.7	0.35

Next I took a closer look at the *SRT*. Again, neglect patients AB and PI were not included in the ANOVA as most of their data was missing for left targets. A 3x2x4 mixed ANOVA with *group* as a between-subject factor and *side* of target and *condition* as the within-subject factor revealed main effects of *condition* ($F_{(2.1,44.2)} = 8.5$, $p<.001$) and *side* ($F_{(1,21)} = 8.2$, $p<.01$) (table 2.25). I found mean reaction times of 248 ms (SE 17.4) for condition 1, 269 ms (SE 15.4) for condition 2, 271 ms (SE 14.5) for condition 3 and 318 ms (SE 18.4) for condition 4 (see also table 2.27). As the assumption of sphericity had not been met for *condition* (Mauchly's W=.473; p< .05) and *condition x side* (Mauchly's W=.257; p< .001), the Greenhouse-Geisser correction was used. The overall mean of the SRT for left targets was significantly longer with 293 ms (SD 16.3) compared to right targets (259 ms; SD 14) (fig. 2.19).

Table 2.25: ANOVA with the factors side, condition and group for the SRT for correct pro-saccades. Significant main effects and/or interactions in italic; * = Greenhouse-Geisser correction for df.

		df	F	Sig.
Within-Subjects Effect	***Condition***	*2.104**	*8.507*	*< .001*
	Condition x Group	4.208*	1.427	.239
	Error (Condition)	44.18*		
	Side	*1*	*8.192*	*.009*
	Side x Group	2	.494	.617
	Error (Side)	21		
	Condition x Side	1.661*	2.143	.140
	Condition x Side x Group	3.322*	.477	.719
	Error (Condition x Side)	34.884*		
Between-Subjects Effect	**Group**	2	.426	.659
	Error	21		

Pairwise comparisons of the four conditions revealed significant differences between condition 4 and condition 1 ($p<.01$; mean difference 70 ms), 2 ($p<.05$; mean difference 49 ms) and 3 ($p<.05$; mean difference 47 ms) with the longest reaction time for condition 4 compared to the other three conditions (fig. 2.20).

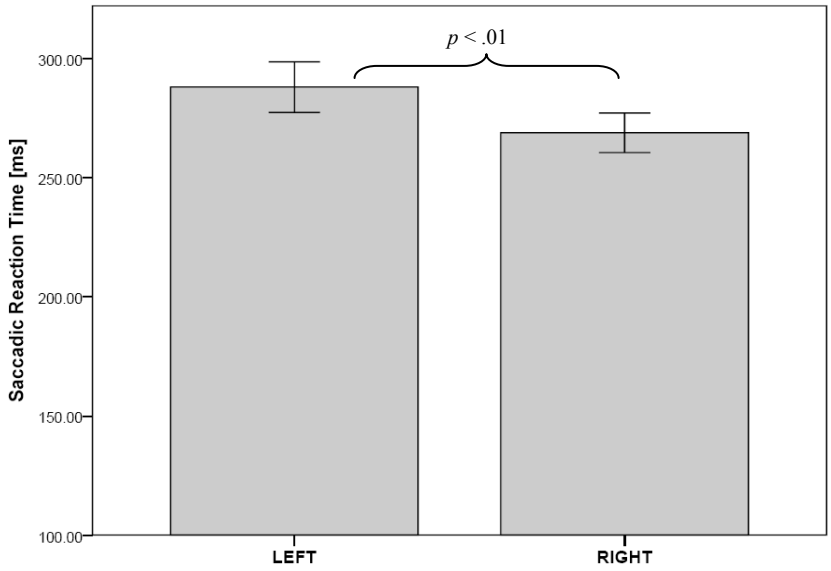


Fig. 2.19: SRT of correct pro-saccades; means for left and right targets. Error bars show +/- 1 SE.

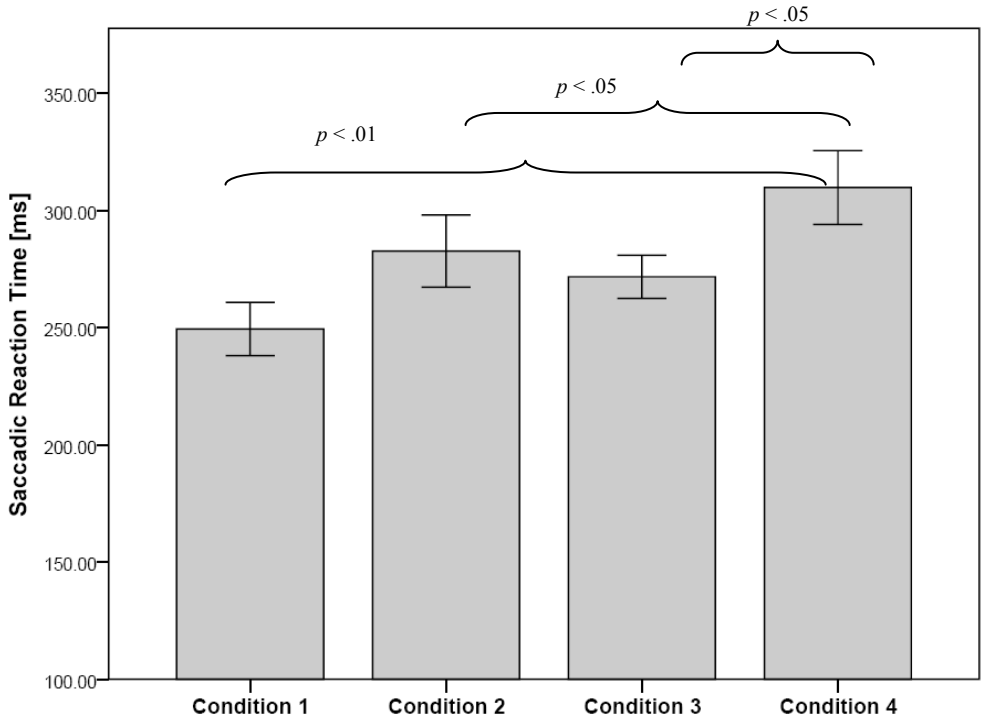


Fig. 2.20: SRT of correct pro-saccades; means for condition 1, 2, 3 and 4. Error bars show +/- 1 SE.

Bearing in mind the absence of a significant group effect, it is no surprise that on an individual level also (see also table 2.26 for all individual and group data), most patients saccaded towards the target stimuli as quickly as the controls. Only patient AB

showed a clear impairment for right targets in most of the conditions. It has to be noted that she almost never responded to left targets but the few saccades she performed were also very slow. Furthermore, patient AK showed slightly longer latencies for most of the right pro-saccades.

Table 2.26: SRT in ms of correct pro-saccades for left and right targets for condition 1 (100% pro-saccades), condition 2 (90% pro-saccades), condition 3 (70% pro-saccades) and condition 4 (50% pro-saccades); group means and individual data.
Significance level for Crawford & Howell's modified t-test (two-tailed): ***=p<.001, **=p<.01, *=p<.05.

			Condition 1	Condition 2	Condition 3	Condition 4
Controls		LEFT	255 (SD 77)	260 (SD 72.6)	274 (SD 61.7)	304 (SD 100.7)
		RIGHT	241 (SD 67.6)	256 (SD 61.5)	254 (SD 58.4)	267 (SD 69.5)
N+		LEFT	259 (SD 120.1)	297 (SD 98.8)	288 (SD 83.6)	407 (SD 168.8)
		RIGHT	244 (SD 96.4)	247 (SD 69.3)	270 (SD 115.6)	331 (SD 149)
N-		LEFT	252 (SD 84.7)	309 (SD 128.6)	277 (SD 45.2)	340 (SD 75.4)
		RIGHT	234 (SD 31.7)	244 (SD 51.3)	265 (SD 37.1)	262 (SD 57.2)
N	**PI**	LEFT	-	-	222	-
		RIGHT	324	396	369	266
	AB	LEFT	80	767***	-	-
		RIGHT	426*	537***	371	586***
	MM	LEFT	161	157	170	168
		RIGHT	248	239	198	220
	JK	LEFT	274	368	332	331
		RIGHT	234	309	364	317
	JH	LEFT	197	241	278	574*
		RIGHT	195	225	231	488*
	AK	LEFT	461*	401	395	401
		RIGHT	401*	316	416*	475*
	JMV	LEFT	202	316	263	559*
		RIGHT	143	147	141	156
N-	**DR**	LEFT	362	387	332	340
		RIGHT	245	276	323	329
	WG	LEFT	314	490**	292	415
		RIGHT	278	234	254	316
	JS	LEFT	230	266	235	328
		RIGHT	239	245	267	213
	RI	LEFT	154	168	225	221
		RIGHT	194	165	220	207
	AMI	LEFT	201	235	299	394
		RIGHT	216	300	260	247

2.3.2.2. Fixation trials

To investigate the participants' ability to inhibit eye movements I analysed the percentage of correct fixations in conditions 2, 3, 4 and 5. While the healthy controls were able to maintain fixation almost perfectly during stop trials [98% (SD 6.7), 96% (SD 9.1), 98% (SD 4.1) and 99% (SD 3.6) for left targets in conditions 2, 3, 4 and 5, and 93% (SD 12.2), 92% (SD 12.7), 97% (SD 5.4) and 98% (SD 3.4) for right targets], the N+ group showed more erroneous pro-saccades in the stop trials and reached 92% (SD 14.3), 83% (SD 32.9), 76% (SD 32.4) and 84% (SD 23.9) correct fixations for left trials, and 76% (SD 26.5), 79% (SD 26.4), 80% (SD 21.3) and 76% (SD 23.7) correct fixations for right trials in conditions 2, 3, 4 and 5. Finally a look at the N- group revealed that they occasionally executed erroneous saccades towards the target. This resulted in correct fixations in conditions 2 to 5 of 78% (SD 21.7), 89% (SD 24.8), 96% (SD 6.3) and 86% (SD 18.2) for left targets and 61% (SD 39.3), 84% (SD 19), 79% (SD 25.1) and 88% (SD 18.1) for right targets (see also table 2.28 for all group and individual data).

A 3x2x4 mixed ANOVA (table 2.27) for the dependent variable *percentage of correct fixations* with *group* as a between-subject factor and *side* of target and *condition* as the within-subject factor revealed a main effect of *group* ($F_{(2,23)} = 10.1$, $p<.001$). As the assumption of sphericity had not been met for the main effect *condition* (Mauchly's W=.552; $p<.05$) and the interaction *condition x side* (Mauchly's W=.574; $p<.05$), the Greenhouse-Geisser correction was used.

Table 2.27: ANOVA with the factors side, condition and group for the correct fixations. Significant main effects and/or interactions in italic; * = Greenhouse-Geisser correction for df.

		df	F	Sig.
Within-Subjects Effect	**Condition**	2.342*	1.401	.255
	Condition x Group	4.684*	2.336	.058
	Error (Condition)	53.87*		
	Side	1	1.718	.203
	Side x Group	2	.174	.842
	Error (Side)	23		
	Condition x Side	2.215*	1.600	.210
	Condition x Side x Group	4.430*	1.122	.358
	Error (Condition x Side)	50.948*		
Between-Subjects Effect	***Group***	*2*	*10.108*	*< .001*
	Error	23		

Pairwise comparisons revealed that the N+ (81% correct fixations, SE 3.2) as well as the N- group (83% correct fixations, SE 3.8) showed significant impairments compared to the healthy controls (96% correct fixations, SE 2.3) with more erroneous pro-saccades towards the target in the fixation trials (N+: mean difference to controls 15.8, $p<.01$; N-: mean difference to controls 13.9, $p<.05$). No difference between the N+ and N- group was found (fig. 2.21).

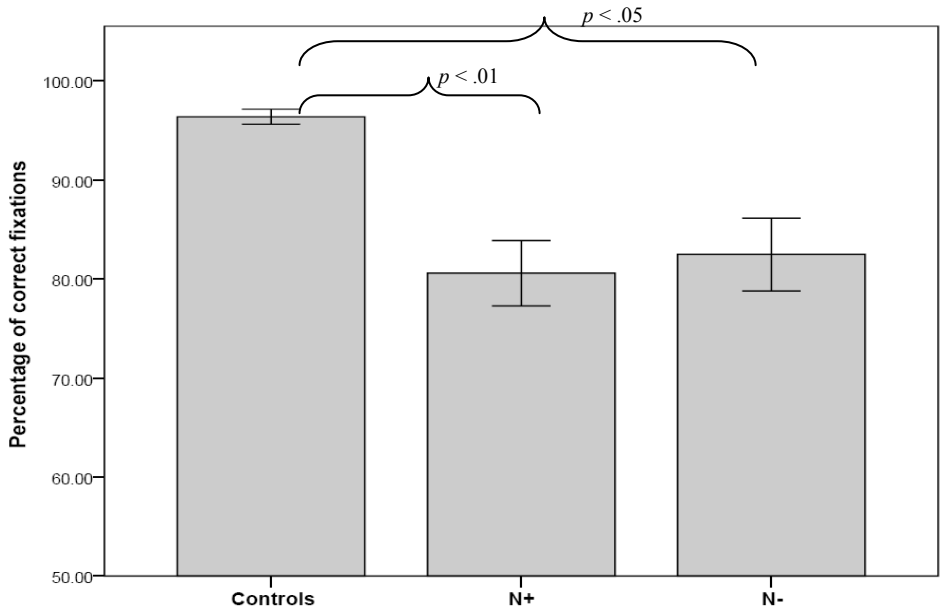


Fig. 2.21: Percentage of correct fixations; means for healthy controls, N+ and N- group. Error bars show +/- 1 SE.

On an individual level, Crawford and Howell's modified t-test (1998) revealed that the ability to withhold saccades varied between the patients with some showing greater deficits for left and others for right targets. In particular N+ patients PI and JMV showed many erroneous pro-saccades towards right targets for all four conditions, while they could perfectly inhibit leftward stimuli. However, PI also almost never saccaded towards left targets in pro-saccade trials. This could be a result of his profound hemispatial neglect. Likewise, N+ patient AB's perfect performance for left targets could be the result of her neglect behaviour as she also almost never responded towards left targets when a pro-saccade was required. Nevertheless, she only showed an inhibition impairment for conditions 4 and 5 while she could perfectly inhibit pro-saccades in conditions 2 and 3. Another patient who showed severe problems for right targets was N-patient WG, while he was able to maintain fixation for left target trials correctly for most conditions. Contrary to these results, other patients showed greater deficits for left targets. Particularly N+ patients MM, JK and JH executed the majority of their erroneous pro-saccades towards left targets, while they showed no (patient JH) or only little (patients MM and JK) impairment for right target fixation trials. Only N-patient DR showed an overall clear impairment. For most conditions, he was not able to inhibit pro-saccades towards left and right targets. For the results of Crawford and Howell's modified t-test and all individual and group data, please see table 2.28.

Table 2.28: Percentage of correct fixations for left and right targets for condition 2 (10% fixation trials), condition 3 (30% fixation trials), condition 4 (50% fixation trials) and condition 5 (100% fixation trials); group means and individual data.
Significance level for Crawford & Howell's modified t-test (two-tailed): ***=p<.001, **=p<.01, *=p<.05.

			Condition 2	Condition 3	Condition 4	Condition 5
Controls		LEFT	98 (SD 6.7)	96 (SD 9.1)	98 (SD 4.1)	99 (SD 3.6)
		RIGHT	93 (SD 12.2)	92 (SD 12.7)	97 (SD 5.4)	98 (SD 3.4)
N+		LEFT	92 (SD 14.3)	83 (SD 32.9)	76 (SD 32.4)	84 (SD 23.9)
		RIGHT	76 (SD 26.5)	79 (SD 26.4)	80 (SD 21.3)	76 (SD 23.7)
N-		LEFT	78 (SD 21.7)	89 (SD 24.8)	96 (SD 6.3)	86 (SD 18.2)
		RIGHT	61 (SD 39.3)	84 (SD 19)	79 (SD 25.1)	88 (SD 18.1)
N+	**PI**	LEFT	100	100	100	100
		RIGHT	50**	33***	42***	90*
	AB	LEFT	100	100	100	100
		RIGHT	100	91	78**	53 ***
	MM	LEFT	67***	9***	12***	33***
		RIGHT	100	75	86	89*
	JK	LEFT	100	89	72***	79***
		RIGHT	75	100	92	86**
	JH	LEFT	75**	89	58***	85**
		RIGHT	100	100	100	100
	AK	LEFT	100	92	95	88*
		RIGHT	75	100	100	78***
	JMV	LEFT	100	100	94	100
		RIGHT	33***	55***	63***	33***
N-	**DR**	LEFT	50***	44***	86***	73***
		RIGHT	89	67	38***	60***
	WG	LEFT	67***	100	100	95
		RIGHT	0***	60*	73***	100
	JS	LEFT	75**	100	94	100
		RIGHT	100	92	94	100
	RI	LEFT	100	100	100	100
		RIGHT	50**	100	89	100
	AMI	LEFT	100	100	100	60***
		RIGHT	67	100	100	78***

2.3.3. Discussion

I showed in the previous experiment (chapter 2.2) that most of the five neglect patients I tested were impaired in executing correct anti-saccades in that, instead of looking in the opposite direction of the target, they looked towards the target. However, although the N+ group was also impaired for the simple fixation task compared to the healthy controls, most of the neglect patients were able to withhold saccades towards the targets, thus showing no general fixation impairment. This additional fixation experiment was then conducted to examine the capability of neglect patients to inhibit eye movements towards peripheral targets in a more complex task. Here I interleaved pro-saccade and fixation trials of varying proportions in different blocks.

It is noteworthy that I had decided to add the recovered neglect patients (patients AK, JK, JH and MM) to the neglect group and my results indeed confirmed that they still showed neglect typical biases in the experimental tasks, e.g. showing lower accuracy for left pro-saccades.

Pro-saccades

This paradigm was previously used by Olk and Kingstone (2009) on healthy younger and elderly participants. Their results indicated that the proportion of fixation and pro-saccade trails within the same block had an impact on the participants' performance. However, comparing the conditions with varying fixation and pro-saccade proportions, I only found a difference regarding the percentage of correct pro-saccades for the N- group with more errors for conditions 2 and 4 compared to the 100% pro-saccade condition in block 1. No differences between the conditions were found for the healthy controls and the neglect patients.

The participants were able to saccade toward the targets in all conditions without showing significantly greater impairment with an increasing of interleaved fixation trials (condition 2: 10% fixation, condition 3: 30% fixation, condition 4: 50% fixation). Looking individually, particularly for condition 1 which consisted of 100% pro-saccades, *no* patients showed impairments for right targets and also for left targets only two neglect patients (PI and AB) and two no-neglect patients (JMV and DR) were impaired compared to the controls. This result is not surprising as previous studies have shown that neglect patients are able to perform target directed on-line actions (e.g. Karnath, Dick, & Konczak, 1997; McIntosh et al., 2001, Butler et al., 2009).

Nevertheless, regarding the overall percentage of correct pro-saccades I found that the N+ group executed fewer correct eye movements towards the peripheral targets compared to healthy elderly control participants. Taking a closer look at the N+ group's performance, I found that the group was particularly impaired for left targets with many omissions, although various studies have reported that neglect patients were able to saccade towards left targets (e.g. Harvey et al., 2002; Butler et al., 2009).

On an individual level most of the neglect patients in my study were indeed able to respond towards left targets but two of the patients (acute neglect patients PI and AB) almost never saccaded towards left targets. Both seemed to almost completely ignore left targets, which was possibly the reason for the N+ group to be significantly worse than the healthy controls. On the other hand, these two patients were able to saccade towards right targets which indicates that they had understood the task.

Next I looked at the accuracy of the correctly executed pro-saccades. The results show that neglect patients showed a clearly decreased accuracy for left targets, while they accurately saccaded towards right targets. Also, neither the healthy control nor the N- group showed lateral biases to targets on one side. No accuracy difference between

left and right targets was found for these groups, thus giving evidence for the leftward bias observed in the experiment being neglect specific.

On an individual level, almost all N+ patients (except JK und AK) showed a reduced accuracy for left targets. Again patients PI and AB were most impaired with the few saccades they executed towards left targets being more inaccurate than for any other participant. Nevertheless, their accuracy for right targets was very good. Likewise, all other N+ patients were able to saccade towards right targets very accurately.

Butler et al. (2009) reported similar results with saccades towards left targets falling too short during pro-saccade conditions. Also Niemeier and Karnath (2003) have found that neglect patients tend to make smaller saccades towards left targets in stimulus-driven conditions. Therefore it is very likely, that the patients in my experiment reached the target after two or more eye movements, but as I only looked at the first saccade, I can only assume this. Furthermore, most of my N+ patients, except PI and AB, showed the same response pattern towards left targets than the previously reported five neglect patients of my first experiment. Most of them indeed saccaded towards right *and* left targets, but the leftwards eye movements had a low accuracy and clearly missed the target. The results show that, as previously reported (e.g. Karnath, Dick, & Konczak, 1997), neglect patients are able to perform on-line actions but I assume that the hemispatial neglect is interfering with the saccade accuracy towards left targets.

However, apart from the neglect patients, N- patients DR and WG also showed impairment in the pro-saccade trials with decreased percentages of correct pro-saccades and decreased accuracy compared to the healthy control group. Both patients showed greater difficulties particularly for left targets as well for right targets. It should be noted that patient DR, who is the more impaired of the two N- patients, scored very low in the BADS, revealing that he might have problems in mental flexibility, showing a tendency

towards perseveration. In fact mental flexibility is required in my experimental task because the interleaved pro-saccade and fixation trials require a quick and continuous decision making, deciding which response is required for each upcoming trial. Therefore it could be possible that DR's impairment showed difficulty in quickly choosing the correct response in answer to the red or green central dot, i.e. whether a fixation or a pro-saccade would be required.

Olk and Kingstone (2009) further examined the influence of interleaved trials and they found longer pro-saccade reaction times, the higher the percentage of interleaved fixation (or anti-saccade) trials was within the block. Thus for interleaved conditions they found the longest pro-saccade reaction times when only 50% of the trials were pro-saccade trials and the shortest saccadic reaction times when 90% of the trials were pro-saccade trials.

Only for my N- group did I find an effect of the different fixation – pro-saccade proportions on the saccadic reaction times that was similar to Olk and Kingstone (2009). The longest reaction times occurred for pro-saccades in condition 4 (50% pro-saccades, 50% fixation). All other conditions showed significantly shorter reaction times for correct pro-saccades compared to the pro-saccades in condition 4. However, unlike Olk and Kingstone I did not find a significant difference between all conditions but only for condition 4 in comparison to conditions 1, 2 and 3.

From the SRT results it seems that the amount of correct pro-saccades occurred at the cost of increased reaction times. As half of the trials in condition 4 were fixation trials, it was more likely that the next trial would be a fixation trial than in condition 2 for example, where only 10% of the trials required a fixation. Thus the participants might have responded more slowly to make it easier to respond correctly and to avoid erroneous pro-saccades.

Fixation

While I previously looked at a simple inhibition task (experiment 1, 2.2) and found that most neglect patients were able to inhibit stimulus-driven eye movements toward left and right targets, I conducted a more difficult fixation task that required cognitive flexibility. Additionally in one of the conditions, I tested the participants with a simple fixation task, similar to the one used in chapter 2.2.

My results revealed a not neglect specific impairment for the N+ and N- group compared to the healthy controls. Both patient groups executed occasional erroneous pro-saccades towards the suddenly appearing target. Apart from PI and AB, who almost never responded to any of the left targets in the pro-saccade trials, I can assume that the other patients inhibited the eye movement as they were able to execute pro-saccades towards left and right targets when it was required.

Olk and Kingstone (2009), who used the same interleaved paradigm to compare healthy elderly and younger participants, reported increased error rates for fixation trials with an increasing of pro-saccade percentages within the same block. In contrast to this, I could not replicate these findings for any of my three subject groups. No significant differences in the amount of erroneous pro-saccades during fixation trials were found between the conditions, indicating that the participants I tested did not experience greater difficulties in withholding a saccade when only 10% of the trials required a fixation (condition 2) than in condition 5 that consisted of 100% fixation trials.

On an individual level N+ patient JMV showed many erroneous pro-saccades towards right targets in the interleaved conditions (condition 2-4) and also in the simple fixation condition (condition 5). I view these errors as neglect typical biases, as various studies have reported neglect patients showing a bias for ipsilesional targets (e.g. Niemeier & Karnath, 2003). As JMV was able to inhibit saccades to left targets, I suppose he had understood the instruction but might have had difficulties to ignore

ipsilesional targets. Very similar response patterns were found for N+ patient PI who executed many erroneous pro-saccades towards right targets in all conditions. However, although he perfectly inhibited left targets in all conditions, I cannot say anything about his general ability to inhibit, as he showed typical neglect behaviour and also never responded to left targets in pro-saccade trials. Two other neglect patients who showed an almost consistent impairment with many erroneous pro-saccades were MM and JH, although both were mostly impaired for left targets, the usually neglected side. However, both had no problems to inhibit eye-movements towards right targets, thus showing that they were able to control their saccades.

Importantly though, analyses revealed that the inhibition problem was not neglect specific. While the pro-saccade impairments of more leftward omissions and greater eye movement inaccuracy were specific for the N+ group with the N- group performing without problems like the controls, both stroke groups (N+ and N-) showed difficulties for the fixation trials. Compared to the healthy controls, N+ as well as the N- patients executed significantly more erroneous pro-saccades when instead they should have inhibited the eye movement.

The individual performance of the N- patient revealed that WG was only impaired for right targets in the interleaved conditions, while he could perfectly withhold erroneous pro-saccades in the simple fixation condition (condition 5). I can thus assume that the increased complexity of the interleaved conditions had an impact on him, although he performed well in the BADS previously, showing no signs of perseveration tendencies or mental inflexibility. However, his lesion is in the basal ganglia, one of the regions that has previously been identified to play a role in cognitive flexibility (Leber, Turk-Browne & Chun, 2008). This might be the reason for his impairment in the interleaved trials but not in the simple fixation condition.

Patient DR also revealed a great overall impairment for stop trials. He made many erroneous pro-saccades to left and right targets. He not only performed very poorly in the interleaved conditions, which is in line with his severe problems in the BADS and basal ganglia lesion, but he was also impaired in the simple fixation condition. This result lets me assume that not only his mental flexibility is affected but also his general inhibition ability.

Finally a closer look at the individual lesions of the N+ patients revealed that lesions to various areas resulted in a fixation impairment and a great number of my patients even showed problems to inhibit saccades during the 100% fixation condition. Severe inhibition problems were found in PI, JH and JMV, whose extended lesions involved the frontal, temporal and parietal lobes. MM, who also showed a clear impairment, has a dorso-frontal and parietal lesion, while JK's lesion involved the frontal and temporal lobes. Furthermore, AB had a temporo-occipital lesion. The variety of the lesion locations makes a conclusion difficult. Indeed, previous studies have found that various brain areas are involved in inhibition processes. For example the frontal lobe as well as more posterior brain areas like the parietal lobe are crucial for occulomotor control and inhibition processes (e.g. Petit et al., 1999; Brown, Vilis & Everling, 2007). Furthermore Butler et al. (2006) also reported a patient with a temporo-parietal lesion who was unable to inhibit task irrelevant distractors and more subcortical structures like the basal ganglia (N- patients DR and WG) seem to play a crucial role. However, WG also has a fronto-temporal lesion and DR showed a general poor performance in cognitive flexibility tasks which could also be the reason for his impairment in this complex fixation task.

Conclusion

The basic idea for this interleaved fixation task was the examining of the ability to inhibit eye-movements and with that, to shed light on the question as to why neglect patients show bilateral errors for anti-saccades (Butler et al., 2009, see also 2.2.). In a previous experiment (chapter 2.2) I found that the majority of neglect patients were able to control their eye-movements in so far that they could withhold saccades towards a target without too many problems. Here I extended the experimental setting by not only testing healthy controls and stroke patients with neglect but also stroke patients without neglect. Furthermore, instead of a simple condition with 100% fixation trials, I used experimental blocks with varying proportions of interleaved pro-saccade and fixation trials to examine the ability of inhibiting eye-movements during more complex tasks.

While for pro-saccade trials the N+ group showed the neglect typical impairment for left targets, the deficits for fixation trials were not neglect specific. Both patient groups made more erroneous pro-saccades compared to the healthy controls. However, most of them did not show a general failure to inhibit saccades but were only impaired in some conditions while they performed perfectly in other conditions, yet compared to the almost flawlessly performing healthy controls they appeared to have deficits. Nevertheless, I suggest that the performance of the stroke patients does not show a general severe inhibition failure. Even during the most difficult conditions with only 10% of the trails requiring a fixation and 90% pro-saccades, they did not fail completely (but nevertheless they still performed worse than the control group).

From this result I assume that the previously found bilateral anti-saccade failure (see 2.2. and Butler et al., 2009) is more likely to be a vector inversion, i.e. off-line action, error than an inhibition problem. Examining the behaviour of neglect patients it has been assumed that off-line errors are possibly caused by lesions to the ventral stream and connecting areas like the IPL (Milner & Goodale, 2006) and the middle and

superior temporal lobe (Rossit et al., 2011). Indeed, most of my patients with lesions to the IPL showed no general inhibition failure. For example JH was only impaired for left and JMV only for right targets. Furthermore Rossit et al. (2011) have previously found that middle and superior structures of the temporal lobe are involved in anti-pointing errors and JK who has a fronto-temporal lesion and AB who has a temporo-occipital lesion, are able to inhibit most of the saccades and show only impairments is some of the conditions, again suggesting these errors to be an off-line action rather than inhibition problem.

Therefore these results could provide evidence for neglect patients being able to inhibit saccades when required and that the anti-saccade errors are indeed rather a remapping problem than an inhibition problem. However, this is only a speculation as I can't make any statements about the actual anti-saccade performance of these patients to see if they are indeed impaired in anti-saccades. Also I believe that this kind of interleaved task requires not only the ability to inhibit eye movements but also cognitive flexibility. The response required for the next trial was unpredictable and the signal to indicate if it was a pro-saccade or a fixation trial appeared only at the moment when the target appeared, thus requiring a quick decision to choose the right action. I indeed found the most severe impairment for the interleaved fixation and pro-saccade trials for patient DR who was previously identified with the lowest BADS score. He not only missed many pro-saccades but also failed to inhibit saccades in the fixation trials. However, as most of the patients I scanned for cognitive flexibility prior to testing, performed almost perfectly in the BADS I cannot make any certain statements about the influence of cognitive flexibility on the interleaved tasks.

2.4. General conclusion

Butler and his colleagues (2009) first asked the question if the bilaterally found anti-saccade errors in neglect patients were the result of an inhibition or a vector inversion problem. To approach this problem I replicated their experiment and added a fixation condition to the previously used pro- and anti-saccade condition (experiment 1). For the pro- and anti-saccades I found similar results to Butler et al. The patients showed neglect typical leftward impairments for pro-saccades with saccades showing a low accuracy and bilateral deficits for the anti-saccades with many erroneous pro-saccades towards the target instead of away from it. The additional fixation task revealed that the neglect patients were also impaired for the fixation task but on an individual level it was only one patient who was severely impaired for both target sides. Most of the tested neglect patients were indeed able to withhold eye movements towards the targets and did not show signs of a general inhibition problem. Besides two patients who performed perfectly, only one patient was very slightly impairment for left targets and another one showed a few erroneous pro-saccades towards right targets. However, most of the patients who showed none or only minor problems in the fixation task were impaired in the anti-saccade task. Therefore I conclude that the reason for the high number of erroneous pro-saccades in the anti-saccade condition might not be the result of an inhibition failure but rather a problem to remap the target location to the opposite side.

To corroborate my finding, a second, more complex fixation task was used in a further experiment with interleaved pro-saccade and fixation trials. Besides stroke patients with hemispatial neglect I also tested patients without neglect for this experiment to reveal if impairments (if there were any) were neglect specific. The results showed that both patient groups performed worse than the controls, yet they were able to withhold most erroneous pro-saccades. Thus I suggest that their

impairment compared to the control group does not reflect a general severe inhibition problem. It is likely that the higher error rate for the patients in this task reflected the greater demands of the task. Unlike the previous simple fixation task I explained in chapter 2.2, the follow-up task in chapter 2.3 did not only require the ability to inhibit eye movements but also cognitive flexibility as the fixation trials were interleaved with pro-saccade trials. Furthermore, no difference was found between N+ and N- patients.

Compared to the very poor anti-saccade performance of the neglect patients with erroneous pro-saccades for more than half of the anti-saccade trials (calculated as a general mean across all patients for left and right targets), most N+ patients were able to inhibit almost all saccades in the simple fixation task (2.2) and were also able to correctly maintain fixation in nearly 80% (general mean across all patients for left and right targets) of the fixation trials of the more complex task (2.3). Therefore I suggest that the data of this second experiment provides more evidence for the bilateral anti-saccade failure being a vector inversion deficit rather than an inhibition problem.

This conclusion would support the second interpretation of Butler et al. (2009): as reported earlier, Butler and colleagues found that their patients produced a great amount of erroneous pro-saccades in the anti-saccade task, i.e. they looked towards the target instead of away from it in the anti-saccade condition. Butler and colleagues suggested therefore, that the patients either had a problem in inhibiting the reflexive saccades or that they were impaired in remapping the target location to the opposite side. My data make the second interpretation more likely.

It is further in line with previous assumptions that the ventral stream processes off-line actions and that several structures like the IPL which is frequently damaged in hemispatial neglect (e.g. Vallar & Perani, 1986; Mort et al., 2003; Karnath et al., 2004) may also display off-line function (Milner and Goodale 2006) and see also Rossit et al. (2011) for further support of this idea for temporal structures. Indeed as described in the

Conclusion previously, most of the patients with inferior parietal and temporal lesions had no general inhibition problems, yet as they were not tested on the anti-saccade task, their data lend only very indirect support to this hypothesis.

Previous studies on visual form agnosia patient DF have already shown that lesions to the ventral stream result in an impairment of delayed or pantomime actions (e.g. Dijkerman, Milner & Carey, 1997; Carey et al., 2006; Rossit et al., 2010). For several years, patient DF who has a lesion to the ventral stream while her dorsal stream remains intact, has been tested repeatedly on on-line and off-line tasks. In line with her ventral stream lesion she has shown a consistent impairment for off-line actions like for example for delayed pointing (Dijkerman, Milner & Carey, 1997; Rossit et al. 2010). It has now been shown that neglect patients show similar performance to patient DF and that they are often impaired in off-line actions (e.g. Rossit et al. 2009b, 2011). However, based on the participants I tested, I cannot make any further predictions about off-line actions regarding particular brain areas as I tested only five patients with anti-saccades (first experiment) whose lesions were very diverse and only two of these patients had lesions in influenced areas. Testing further patients with lesions to the ventral stream or areas that Milner and Goodale (2006) speculate to be functionally connected like the IPL or the superior or middle temporal lobe (as implicated by Rossit et al., 2009a, 2011) would help to gain more information about the involvement of ventral stream type processes in the bilateral vector inversion failure in anti-saccades.

Also it has to be mentioned, that from my results I cannot conclude if the bilateral anti-saccade deficits are neglect specific or would also apply to stroke patients without neglect. No difference was found between neglect and no-neglect patients for the fixation trials in the interleaved fixation and pro-saccade tasks (experiment 2) but I did not test no-neglect stroke patients on anti-saccades. From Rossit et al.'s (2011) findings that no-neglect patients performed well in the anti-pointing tasks while neglect

patients showed problems, it can be assumed that no neglect right hemisphere lesioned stroke patients might be able to perform anti-saccades and would not show significantly more erroneous pro-saccades than the healthy controls.

More detailed investigations into the ability to perform anti-saccades are also necessary. So far, Butler et al. (2009) and I used anti-saccade tasks with only two locations. To get a more detailed view of the anti-saccade performance, the task would benefit from targets that are not only located on a horizontal meridian but also vertically or with different distances to the central fixation point for example.

In summary, my investigation into the fixation performance of the neglect patients allowed me to assume that inhibition problems are not likely to be the reason for the anti-saccade failures. However, I cannot draw any firm conclusions about the anti-saccade deficits being an off-line remapping, vector inversion deficit as too few patients were tested on both fixation and anti-saccade tasks and more patients with either inferior parietal or temporal lesions will have to be tested on both of these tasks. However, I can tackle this question more directly by discussing patient DF's performance in a pro-saccade, anti-saccade and fixation experiment which I will do in chapter 4.

Chapter 3

ON-LINE AND OFF-LINE PERFORMANCE IN HEMISPATIAL NEGLECT: MEMORY-GUIDED SACCADES AND ON-LINE CORRECTIONS

3.1. Introduction

As described in the first 2 chapters, over the last 15 years, Milner and Goodale (1995, 2006, 2008) have proposed and refined an influential theory that distinguishes between the visual ventral stream and the visual dorsal stream. Crucially they have argued that these two visual streams operate on different time scales: the ventral stream represents a target object long-term. This allows object characteristics to be maintained over time and therefore aids object recognition across different viewing conditions. The dorsal pathway works in real-time for immediate use in guiding actions.

Strong evidence for this model comes from patient DF, who suffers from visual form agnosia after bilateral damage to the ventro-lateral occipital region, sparing V1, thus her lesion is supposed to affect her visual ventral pathway (see also chapter 4). Testing of patient DF has repeatedly shown that she is normal in immediate reaching and grasping (Goodale & Milner, 1992; Goodale, Jakobson & Keillor, 1994; Milner & Goodale, 1995), yet severely impaired when asked to perform delayed actions (Goodale, Jakobson & Keillor, 1994; Milner & Goodale, 1995; Milner, Dijkerman & Carey, 1999). More recently, as described in chapter 1, Rossit et al. (2009b) have found a similar dissociation in patients suffering from hemispatial neglect. In this chapter I want to test if this dissociation can also be demonstrated for oculomotor behaviour. Moreover, I will test the ability of neglect patients to perform oculomotor on-line corrections towards perturbed targets. I have already described in chapter 1 that for reaching, automatic on-line corrections are relatively spared in neglect patients (McIntosh et al, 2010) and I thus expect neglect patients to be able to perform oculomotor on-line corrections in perturbed trials. In the rest of the introduction I will give a more in depth background and rationale for these two experiments.

3.1.1. Delayed performance

From single-unit electrophysiology in the macaque it has long been known that neurons in the monkey PPC, in the LIP in particular, are not only responsive to the onset of a stationary stimulus in the receptive field (Colby, Duhamel & Goldberg, 1996) but also show response enhancement when attention is drawn to a stimulus without looking at it. Moreover Goldberg et al. (2002) who examined six rhesus monkeys with memory-guided saccades found LIP neuron activity throughout the delay period in a memory-guided saccade task and LIP activity in response to distractors that flashed outside the receptive field during the delayed period.

Various studies have in fact shown delay-period activity during memory-saccade tasks (e.g. Gnadt & Anderson, 1988; Barash et al., 1991) and LIP neurons not only respond when a sensory stimulus is presented but also while the memory of that stimulus is maintained (Colby & Duhamel, 1996; Goldberg et al., 2002). Colby and Duhamel (1996) recorded from single LIP neurons. In their task, rhesus monkeys were trained to look at a central fixation point while a target stimulus appeared outside the receptive field of the neuron. As the stimulus flashed only briefly it was not longer visible when the monkey saccaded to the location where it had appeared. However, the neuronal response to the memory trace of the previous stimulus let Colby and Duhamel to conclude that LIP neurons encode spatial locations and remap the memory trace of a previous stimulus event.

In addition neuroimaging studies of the human PPC have revealed potentially homologous regions, with numerous reports of sustained activity in this area during a delay period, before subjects make saccades (Connolly et al., 2002; Curtis & D'Esposito, 2006). In Connolly et al.'s (2002) study, participants had to perform pro- and anti-saccades towards or away from a peripheral target. They used two conditions: a gap condition and a delay condition. While in the gap condition a peripheral target

appeared after a delay of 0s, 2s or 4s, it appeared immediately in the delayed condition but here the participant had to wait 0s, 2s or 4s for a go signal to make a saccade. FEF and IPS activity was found for the delay interval in the delay condition but FEF activity only for the delay interval in the gap condition, indicating a contribution of the IPS to memory-related responses.

Various other studies have presented comparable results implicating the IPS in memory-guided saccades and it has been found that its activity decreased once the response to a target location was known or selected (Curtis, Rao & D'Esposito, 2004; Curtis & D'Esposito, 2006). The task in Curtis and D'Esposito's study (2006) consisted of four targets that briefly appeared around a fixation dot. This was followed by a first delay interval in which only the fixation dot was visible. Next a cue pointed to one of the previous target locations but only after a second delay interval, was the participant allowed to saccade towards the memory-guided target location. The fMRI data showed FEF and IPS activity during the first delay period that was associated with response selection, but FEF activation only was visible in the second delay interval after response selection to a target location. These results give further evidence for the IPS playing a crucial role in memory for spatial locations and the FEF being involved in conducting the saccade once the location is selected (Curtis, Rao & D'Esposito, 2004). Moreover Schluppeck et al. (2006) and Schluppeck, Glimcher and Heeger (2006) have recently presented the first clear evidence that topographically organised areas in the human PPC, in particular around the IPS, show sustained lateralized delay-period activity for memory-guided saccades. They argue that these areas may be potential homologues of monkey LIP.

Further supporting evidence for the involvement of human PPC in memory-guided saccade processing comes from both single and double-pulse TMS. Müri et al. (1996) showed in their memory-guided saccade study on eight humans that single-pulse

TMS applied over the right PPC, in the delay period, increased the amplitude error of the contralateral memory-guided saccades. They used a memorisation delay of 2,000 ms after a laterally flashed target and applied TMS at different time intervals in the delay period. They found that TMS applied over the right PPC at 260 ms after the target was presented, impaired the performance accuracy, suggesting that the PPC might be involved in early stages of saccade processing, i.e. saccade amplitude preparation in the sensorimotor processing period. Also double-pulse TMS over the right PPC shortly before saccade onset provoked a hypermetria of contralateral memory-guided saccades (Nyffeler et al., 2005).

In summary, various studies agree with the involvement of the PPC in memory-guided saccades. Particularly the important role of the IPS in humans, which is thought to be homolog to the monkeys' LIP (Schluppeck et al., 2006; Schluppeck, Glimcher & Heeger, 2006), has been confirmed repeatedly in neuroimaging and TMS studies (e.g. Müri et al., 1996; Curtis, Rao & D'Esposito, 2004; Nyffeler et al., 2005; Curtis & D'Esposito, 2006).

3.1.2. The involvement of the dorsal and ventral stream in delayed and immediate responses

Although various studies have found evidence for PPC involvement in memory-guided saccades, Milner and Goodale (e.g. 1995, 2006) proposed that areas outside the PPC are involved in delayed responses. According to their theory, the dorsal stream processes immediate (on-line) actions and the ventral stream is involved in memory-guided (off-line) performances. So far the evidence for this comes largely from reaching and grasping but not oculomotor studies.

Westwood and Goodale (2003) had participants grasp a target and results showed that the occlusion of this target in the moment the response was cued (off-line trials), resulted in decreased accuracy. On the other hand, they performed better in on-line trials in which the target object was visible. The authors concluded that the separate visual pathways are responsible for the different performance. In trials in which the target is visible at the time the cue is presented and a response is required, structures of the dorsal stream, e.g. the PPC, are involved. On the other hand, if the target is not visible when the response is cued, Westwood and Goodale argue that the ventral stream takes over and uses stored representation. They suggested an immediate change from dorsal to ventral stream processing once the target is occluded. Himmelbach and Karnath (2005) agree that the dorsal stream processes on-line and the ventral stream off-line actions but unlike Westwood and Goodale, they propose a more gradual change between the streams.

Moreover, Cohen et al. (2009) found evidence for the dorsal stream contributing to the on-line control of grasping an object and they reported that both streams are needed to perform memory-guided grasping. They applied TMS during immediate and delayed grasping tasks over dorsal and ventral stream structures, namely the anterior IPS and the LO cortex respectively. In accordance with Milner and Goodale's model, which proposes that the ventral stream represents a target object long-term and plays a role in memory-guided action, they found that TMS over the LO caused deficits in delayed action. Furthermore, TMS over the anterior IPS resulted in impaired performance in immediate and delayed trials.

Further evidence for the role of dorsal and ventral stream structures in immediate and delayed actions comes from lesion studies. Visual form agnosia patient DF, who has a lesion to the ventral stream while her dorsal stream remains mostly intact (James et al., 2003), has repeatedly shown an impairment for delayed, off-line action,

while she shows no deficits for immediate, on-line performances (e.g. Goodale, Jakobson & Keillor, 1994; Milner & Goodale, 1995; Carey et al., 2006; Rossit et al., 2010; see also chapter 4). In contrast to this, patients with optic ataxia, whose lesions frequently involve the PPC (e.g. Karnath & Perenin, 2005), an area which is part of the dorsal stream, perform well in delayed actions but show an impairment for immediate actions (Milner et al., 1999; Milner et al., 2001).

For immediate actions, Goodale, Jakobson and Keillor (1994) found that optic ataxia patient RV had great difficulties to grasp an objects correctly while it was visible, while visual form agnosia patient DF showed no problems to pick up objects. Milner and colleagues (e.g. 1999; 2001; 2003) also found evidence that optic ataxia patients improve when they can use memorised information to complete a task. Patient IG for example showed an increased accuracy of her grip aperture when she had to delay her grasping movement compared to immediate grasping trials (Milner et al., 2001). Furthermore, they also found that optic ataxia patients used memorised information to execute stimulus-driven, on-line responses.

Only recently have researchers of neglect patients attempted to place the syndrome of spatial neglect in the dorsal-ventral-stream dichotomy, yet some studies have reported that neglect patients show a similar performance to patient DF in on-line and off-line tasks. For example Rossit and colleagues (2009b) found impaired accuracy when neglect patients had to point towards remembered leftward locations while they did not show any deficits when they had to perform immediate pointing movements towards targets. Likewise, other studies have shown that neglect patients are not impaired in on-line performances like simple pointing tasks towards visible targets (e.g. Karnath, Dick, & Konczak; 1997; Himmelbach & Karnath, 2003) and reaching and/or grasping tasks towards single objects (e.g. Chieffi et al., 1993; Pritchard et al., 1997; Milner, Harvey, & Pritchard, 1998). So although some neglect patients may suffer from

PPC and in particular IPS lesions, the typical damage tends to be more inferior to the IPL and temporal lobe (Mort et al., 2003; Karnath, Ferber & Himmelbach, 2001; Rossit et al., 2009a) so if Milner and Goodale are correct such patients should also be relatively more impaired in performing memory-guided compared to immediate saccades. This is something that has not been investigated before and that I will address in the first experiment of this chapter.

3.1.3. On-line corrections

On the other hand, my hypothesis is that neglect patients should be able to perform saccadic on-line corrections. Whilst many studies have employed stationary targets, others have investigated on-line motor control performance by using targets that suddenly and unpredictably change their location (e.g. Pisella et al., 2000; Blangero et al., 2008; Gaveau et al., 2008). Responses to perturbed targets require the alteration of a simple goal directed action, as the task parameters suddenly change during the course of the trial. It has been shown that fast on-line corrections can be done during reaching movements towards targets that suddenly change position (Goodale, Pelisson & Prablanc, 1986) or orientation (Desmurget et al., 1996). A swift and correct adjustment of the response was observed even when the participant did not recognise the actual change of the target (e.g. Goodale, Pelisson & Prabanc, 1986; Pelisson et al., 1986) and also if any visual information of the hand with which the task was performed was absent (e.g. Goodale, Pelisson & Prabanc, 1986; Pelisson et al., 1986; Komilis, Pelisson & Prablanc, 1993).

Pisella et al. (2000) used a task with interleaved perturbed and unperturbed targets. Participants were instructed to point towards these targets and, depending on the instruction, they either had to interrupt their movement when a jump occurred or, in another condition, to correct their movement and follow the target. Pisella and

colleagues found that healthy volunteers showed a fully automated response and corrected their response towards the jumping target, even when they were told to stop their movement and return to the start point. Further evidence for this automatic behaviour comes from the fact that the corrected movements did not take significantly longer than pointing towards a stationary target. In contrast, optic ataxia patient I.G., who has bilateral PPC lesions, was clearly much slower in the corrective movements in the perturbed trials, when compared to the healthy controls. Furthermore, although she was able to point accurately toward stationary targets, she was slower in these unperturbed trials also. Finally, she did not produce erroneous corrective movements like the healthy volunteers and was able to interrupt her movement.

Blangero et al. (2008) tested on-line corrections to perturbed targets by requesting their participants to point towards a target which was centrally located 27cm away from the starting point at the top of the screen. In 20% of the trials, the centre target jumped either to the left or the right side as soon as the participant moved their hand to point towards it. Blangero and colleagues investigated corrective behaviour in jump trials as well as the saccadic eye movements. They found that most of the corrective responses healthy participants carried out, were preceded by a saccade towards the target. However, no relationship between saccade and correction behaviour was found for optic ataxia patients. Furthermore, the results showed that healthy participants were able to smoothly correct their hand-movement towards the jumping target, while it has been repeatedly reported that optic ataxia patients correct their movement gradually with the first pointing movement ending on the previous target position (Grea et al., 2002).

Another study that investigated eye-hand coordination during a pointing task with perturbed and unperturbed trials was carried out by Gaveau et al. (2008). Two optic ataxia participants with bilateral PPC lesions and five healthy control subjects had

to saccade and point towards a target. In 16% of the trials the target changed position unpredictably while 84% of the trials were unperturbed. In the first experiment the target jump remained unnoticed as it occurred at the onset of the first saccade. While the healthy participants showed a fast visual capture of the target and the pointing movement started before the corrective saccades took place, the optic ataxia patients showed delayed visual capture for the targets (in particular for perturbed targets) and started their pointing movement only after the end of their corrective saccades. However, when the target jump occurred at the end of the first saccade towards the stimulus, thus giving the participants less time for an updating of the target location, healthy controls showed a decreased ability for fast saccadic control as well. Therefore Gaveau and colleagues proposed that the impairment shown in optic ataxia patients results from a lack of fast updating of the target location.

In contrast to this and as described in chapter 1, McIntosh and colleagues have studied target perturbation in patients with visuospatial neglect (McIntosh et al., 2010) and found that they corrected their reaches to right as well as left target jumps, even when told to stop their reach. The occurrence of such uninstructed corrections suggests that the 'automatic pilot' system is functional in neglect and I want to test if this unimpaired function also holds for oculomotor behaviour.

3.1.4. Purpose of the current experiments

As outlined above, Milner and Goodale (e.g. 1995, 2006, 2008) have proposed that the dorsal stream is involved in on-line processes and the visual ventral stream is needed in off-line performances and various studies on visual form agnosia patient DF and optic ataxia patients (e.g. Goodale, Jakobson & Keillor, 1994; Milner et al., 2001), as well as non-patients studies like Cohen et al.'s (2009) TMS study, have given supportive

evidence. While patient DF has been tested repeatedly over the last 20 years and provided valuable evidence, more recently patients suffering from hemispatial neglect have shown similar response patterns to DF with an impairment in off-line tasks and no deficits in on-line tasks (Rossit et al., 2009b, 2011). This is not surprising if Milner and Goodale (2006) are correct in arguing that the IPL, a brain area that is frequently damaged in neglect patients (Mort et al. 2003), is supposed to receive information from the ventral stream (see also Rossit et al., 2009a,b; 2011 for a similar argument for temporal areas). In the last chapter (bearing in mind all the limitations I outline in the discussion of this chapter), I already reported (some limited) evidence for an off-line failure in neglect patients as they were unable to perform anti-saccades. However, they were not generally impaired in on-line tasks (i.e. pro-saccades).

In the current experiments I will now take a closer look at the on-line and off-line performance of neglect patients by using another paradigm, testing their ability to perform delayed, memory-guided vs. immediate, stimulus-driven saccades. With the aim of extending Rossit et al's (2009b) previous results into the oculomotor domain I hope to find neglect patients to be impaired in off-line, delayed saccades but not immediate saccades. While the first experiment mainly focuses on off-line performances, I will conduct a second experiment, in which I will investigate their ability to perform on-line actions, in particular automatic on-line corrections. A more detailed description of the tasks will follow for each experiment in the related sections. For more information about patient DF's performance on these tasks, see chapter 4.

3.2. Experiment 3: Memory-guided saccades (off-line performance)

The memory-guided task was inspired by Rossit et al.'s (2009b) findings that neglect patients were impaired in memory-guided pointing. It has to be noted, that lines that pointed from a central fixation dot into one of six different directions were chosen as targets instead of target dots. Thus the task required the remembering of a direction only, rather than that of a particular location. I chose this slight modification as initial piloting with DF showed that she found it almost impossible to remember specific single targets. As we wanted to be able to compare her performance to that of the neglect patients, we tested the neglect patients on this simplified task too.

The neglect patients are supposed to show a memory-guided performance as in Rossit et al. (2009b), so I predict that they will be significantly impaired in delayed, off-line saccades. I expect them to be unable to remember where the target has appeared. This should result in low saccade accuracy and increased reaction times compared to healthy control participants in particular, especially on the left. In an additional control task I will also test their ability to saccade towards visible target lines. As neglect patients have shown in previous tasks that they are not impaired in on-line performances (e.g. Chieffi et al., 1993; Karnath, Dick, & Konczak, 1997, Rossit et al., 2009b), I expect the neglect patients to be able to execute on-line saccades towards target lines. No difference regarding accuracy and latencies, compared to healthy controls, is predicted.

Finally, I intend to examine the role played by inferior parietal and temporal areas in memory-guided saccades, following the work of Rossit and colleagues who implicated these areas in off-line actions (Rossit et al., 2009a; 2011). Additionally I will examine the role played by other regions such as the IPS.

3.2.1. Method

Healthy participants

12 healthy elderly right-handed subjects (mean age 66.4 years, SD 8.5) participated in the study and were reimbursed for travel expenses.

Patients

Eleven right hemisphere stroke patients took part in the study, seven of which also participated in the oculomotor inhibition experiment (chapter 2.3). From the N+ group patient PI, MM, JH, JK and AK, and from the N- group patient WG and JS took part in both studies. All patients were assessed with the *BIT* (Wilson, Cockburn & Halligan, 1987), *Line Bisection* (Harvey, Milner & Roberts, 1995) and the *Balloons Test* (Edgeworth, Robertson & McMillan, 1998) to identify neglect specific bias. I also tested the patients for visual field deficits and extinction with laptop based tests.

Five of my eleven patients suffered from a visual field deficit with three patients showing a hemianopia for the left visual field and two patients (JG and JS) showing a lower left quadrantanopia. Furthermore, three patients showed extinction.

Five of my patients were identified with neglect (N+ group; mean age 64.2 years, SD 6.9) and another six stroke patients who had never suffered from neglect (N- group; mean age 64.5 years, SD 6.8) took part in the study as well. For a detailed description of these subject groups and the tests that were conducted for assessment, please see chapter 2.

As the experimental task involved remembering the location of a single line that could appear in one of six possible location, all patients were additionally examined with a spatial working memory test (SWM; Malhotra et al., 2005). In this test ten dots (nine of which were black and one was pink) were presented in a vertical line in the

centre of a laptop screen. The pink dot appeared randomly and unpredictably at one of the ten dot locations amongst the nine black dots. After the first line of ten dots was presented for 2,000 ms, a random pattern briefly appeared which was followed by another line of ten dots (again nine black and one pink dot). The participant then had to decide whether the pink dot in the second line appeared in the same location as it did in the first array.

After the first 20 trials, two lines with the pink dot appearing in two different locations were presented and the participants had to remember both locations. Now they had to decide if the pink dot in a third line had appeared in that location before during the first two lines. Gradually, participants had to remember three, four and five locations. The test consisted of five blocks of 20 trials each.

As my experimental task only requires remembering one of six locations at a time, I looked at the first block especially, where the participant had to recall only one location of the pink dot. Eight patients were able to remember 100% of the trials in which they had to recall one location while the other four patients (DG, WG, PI, JH) remembered 95%, 85%, 70% and 50% of the twenty trials in the first block.

Please see table 3.1. (a) and (b) for demographic and clinical details and fig. 3.1 for the lesion locations. Patients were recruited from the Southern General Hospital in Glasgow. The study was conducted in accordance with the ethical guidelines of the South Glasgow University Hospitals NHS Trust and the Declaration of Helsinki. All participants gave their informed consent prior to the study.

Table 3.1 (a): Demographic and clinical data of right hemisphere stroke patients.
Initials of patients who took part in the oculomotor inhibition study (chapter 2.3) are written bold and italic.

PATIENT	GENDER	AGE	SCAN	ETIOLOGY	LESION LOCATION	VISUAL FIELD DEFICIT	EXTINCTION
PI	M	56	MRI	Infarct	fronto-temporo-parietal	YES	YES
MM	F	66	MRI	Infarct	dorsal frontal, parietal, corona radiata	NO	NO
JK	F	72	CT	Infarct	fronto-temporal	NO	NO
JH	F	58	MRI	Infarct	fronto-temporo-parietal	YES	YES
AK	F	69	CT	Infarct	posterior frontal, posterior insular, parietal	NO	NO
JG	M	65	CT	Haemorrhage	basal ganglia	YES	YES
DG	M	60	CT	Infarct	Right MCA, temporal + insular cortex, posterior lentiform nucleus	NO	NO
WG	M	67	MRI	Infarct	Right MCA, basal ganglia and pallidus, temporal + frontal cortex	YES	NO
JS	M	56	CT	Infarct	dorsal frontal, posterior temporal, parietal	YES	NO
AM	M	63	CT	Infarct	lentiform nucleus	NO	NO
JC	M	76	CT	Ischemia	Right MCA, frontal lobe, anterior insula cortex	NO	NO

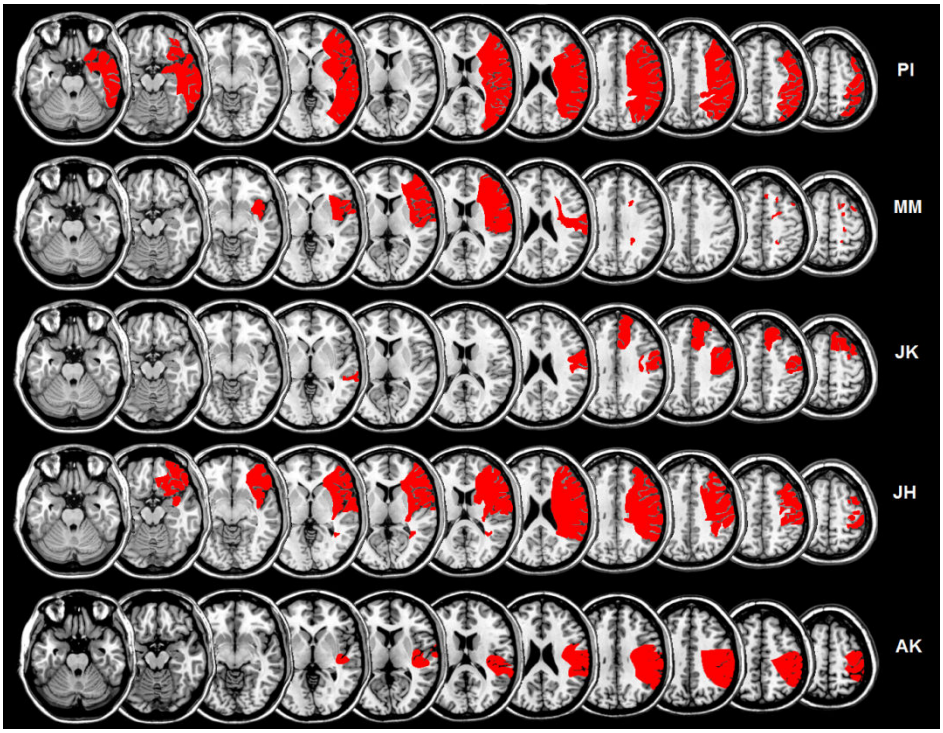
Table 3.1 (b): Clinical data of right hemisphere stroke patients.
Initials of patients who took part in the oculomotor inhibition study (chapter 2.3) are written bold and italic.

PATIENT	TIME SINCE INJURY ONSET 1	LINE BISECTION	BALLOONS	BIT 1	TIME SINCE INJURY ONSET 2	BIT 2	SWM (1^{st} block)	GROUP
PI	5	50	11%	84	-	-	70%	N+
MM	2	3	59%	142	31	144	100%	N+
JK	4	15	44%	141	38	135	100%	N+
JH	10	14	50%	132	43	139	50%	N+
AK	1	16	43%	121	25	142	100%	N+
JG	10	-7.3	64%	136	-	-	100%	N-
DG	3	3.7	50%	144	-	-	95%	N-
WG	3	5.6	50%	143	-	-	85%	N-
JS	14	1	53%	146	-	-	100%	N-
AM	40	3	50%	146	-	-	100%	N-
JC	3	4.8	47%	138	-	-	100%	N-

BIT = Behavioural Inattention Test (cut-off score 129), Line Bisection cut-off score 6; Balloons cut-off score 45%, SWM = Spatial Working Memory Test.
Time Since Injury Onset 1 = time (in months) elapsed when assessed for the first time, but if time between assessment and participating in experiment was too long, patients were retested with the BIT (BIT2), Time Since Injury Onset 2 = time (in months) elapsed when retested; N+ = neglect group, N- = no neglect group

Lesion locations

(a)



(b)

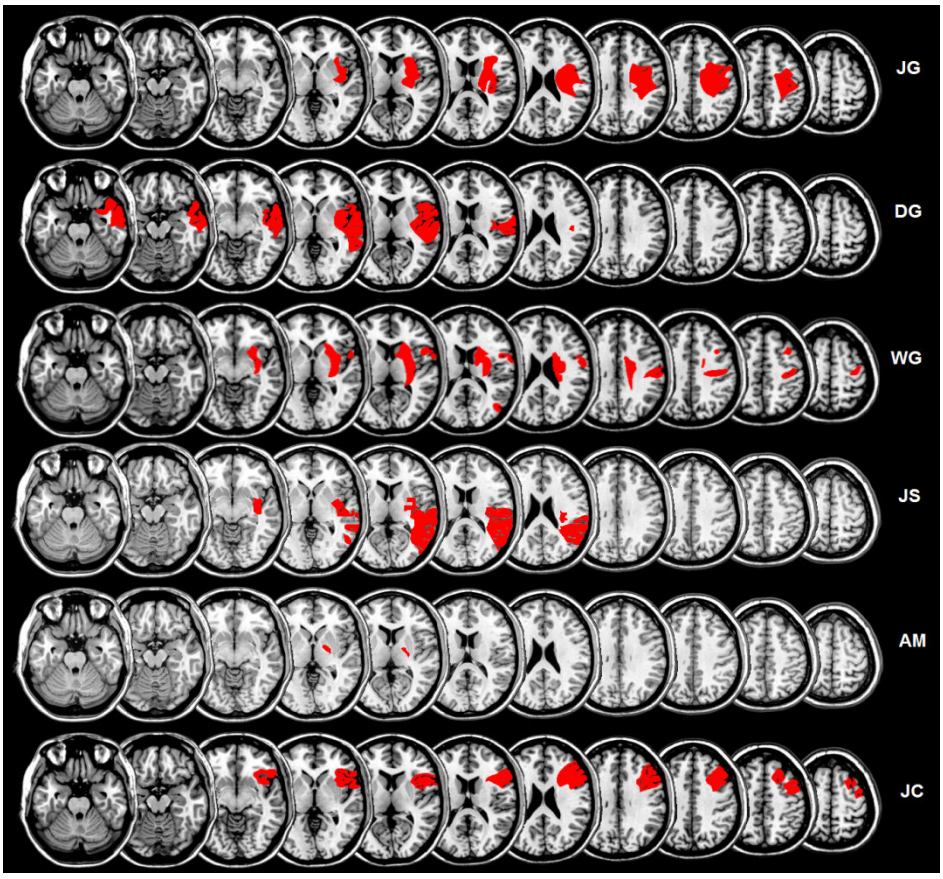


Fig. 3.1: Voxel-based lesion map for each patient with hemispatial neglect (a) and without hemispatial neglect (b) in axial view.

Apparatus and stimuli

A white circle with a diameter of 0.7 degrees was displayed centrally and served as a fixation point. A green circle (same size and location) served as a go signal in the memory-guided condition. Stimuli consisted of white lines, each with a length of 11.2 degrees and a width of 0.2 degrees, which projected from the central circle to one of six possible locations (vertically up, vertically down, or 30 degrees above or below the horizontal midline on either side). A single line was shown in each trial.

The equipment for stimuli presentation and recording was similar to the previous experiment (see chapter 2).

Procedure

The experimental task consisted of three blocks with 66 trials each: two blocks of memory-guided saccades (132 trials) and one block of immediate saccades (66 trials). To avoid practice affecting the memory condition, all participants started with the memory-guided saccades towards the remembered line location, followed by a block with immediate, stimulus-driven saccades towards the line position.

At the beginning of the experiment, the task was explained with the help of 12 practice trials per condition. These trials could be repeated if necessary until the subject had understood the task although this proved not the case for any of the participants. Each of the three blocks of trials started with a nine-point grid calibration and validation procedure (for details please see chapter 2.2).

For each trial, participants were instructed to fixate the central circle. The actual task was manually started by the experimenter via button press, and (to reduce anticipation) after a random delay (1,000 ± 0 – 83.33 ms, in steps of 16.67 ms), a line appeared. In the memory-guided saccade condition, the line was presented for 200 ms. Following offset of the line, the fixation circle remained on the screen and participants

were asked to maintain fixation on the central circle. After 2,000 ms, the white fixation point changed colour to green for another 2,000 ms and the participants had to saccade towards the remembered location (i.e. where the line had been). Each trial ended with the disappearance of the green central circle and after 1,000 ms a new fixation point appeared in the centre of the screen.

The immediate saccade condition was similar to the memory-guided condition but in these trials the line appeared for 1,000 ms. The participant had to make an eye movement towards the line as quickly and accurately as possible, as soon as the line was displayed (the experimenter stressed that to saccade to anywhere on the line was acceptable but to aim for the midpoint). After that, line and central circle disappeared together and the screen went blank for another 1,000 ms until a new fixation point appeared. Each participant had to complete all three blocks. Left, central and right stimuli were counterbalanced within the blocks.

Example displays are shown in figure 3.2.

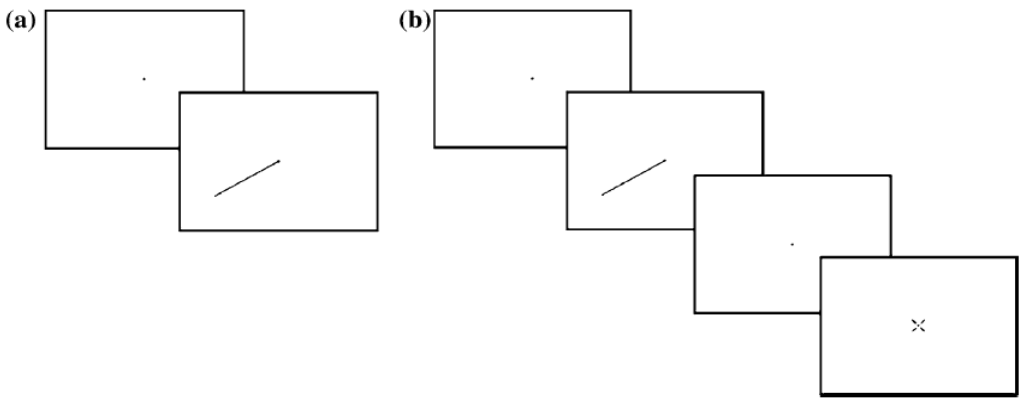


Fig. 3.2: Schematic layout of the stimulus-driven (immediate) and memory-guided (delayed) saccade conditions. In the stimulus-driven condition (a), the participant was required to initiate a saccade towards the line as quickly and as accurately as possible. The line remained visible for 1,000 ms. In the memory-guided saccade condition (b), the line remained visible for 200 ms to be replaced by the fixation circle for 2,000 ms. Following a change in the colour of the fixation circle (indicated by *flash bars*), the participant was required to make a saccade towards the remembered location of the line.

Data processing

Trials on which observers made a saccade with a latency shorter than 80 ms were considered anticipatory and were excluded from further analysis. Also, trials on which the central circle was not properly fixated at the beginning of the trial (deviation larger than 2 degrees) were excluded from analysis. As the participants had to fixate the central dot for more than 2,000 ms before they were allowed to respond to the target in the delayed condition, I used a more generous fixation criterion compared to the studies described in chapter 2. Finally trials with no or too small (shorter than 1 degree) saccades were also excluded.

These criteria resulted in rejection of 12.9% for the stimulus-driven, immediate saccade trials for the healthy controls, 32.4% for the stroke patients with neglect and 17.4% for the stroke patients without neglect. For the memory-guided, delayed saccade trials, these numbers were 19.1%, 45.4% and 31.3% respectively (see Table 3.2 for a more detailed breakdown).

Table 3.2: Percentage of excluded trials for the immediate saccade and delayed saccade trials, presented separately for healthy controls, N+ and N- patients.

		immediate saccades	delayed saccades
Controls	**anticipation**	6.1%	6.5%
	fixation	2%	1.8%
	amplitude	4.8%	10.5%
N+	**anticipation**	16.1%	16.5%
	fixation	2.4%	9.5%
	amplitude	13%	16.4%
N-	**anticipation**	6.8%	13.5%
	fixation	1.8%	3.1%
	amplitude	8.3%	13.9%

3.2.2. Results

For the analyses only the first saccade after stimulus onset was used. The data were analysed separately for leftwardly, centrally and rightwardly presented stimuli by combining the data from the two lines located in that section of the screen, i.e. the two lines which pointed to the left side, the two lines which pointed centrally up and down and the two lines which pointed to the right.

For group analyses, the participants were separated into 3 groups: healthy controls (twelve subjects), patients with neglect (N+; five subjects) and patients who never showed neglect (N-; six subjects). The statistical analyses were done with SPSS using repeated measures ANOVA and post-hoc pairwise comparisons were done with Bonferroni adjustment ($p<.05$). To take a closer look at the individual data, a modified t-test (Crawford & Howell, 1998) was applied, using the two-tailed significance level. This test allows the comparison of a single patient to a sample of control subjects (see also chapter 2.2).

As mentioned earlier, prior to the experimental task I had tested my patients with the SWM test (Malhotra et al., 2005). While most of the patients had no problems to remember one of ten possible locations correctly, four patients were impaired to recall the location. To test if their inability to remember a single location (out of ten possible locations) had an effect on their performance in my experimental task, in which they had to remember the position of a line (out of six possible positions), I correlated the SWM test score (see table 3.1 b) with the mean percentage of correct memory-guided saccades towards a line (see table 3.4). A positive and significant correlation of $r=.623$ ($p<.05$, two-tailed) was found, using Spearman's rho correlation, indicating that patients who scored low in the SWM also tended to perform poorly in the memory-guided condition of the experimental task (fig. 3.3).

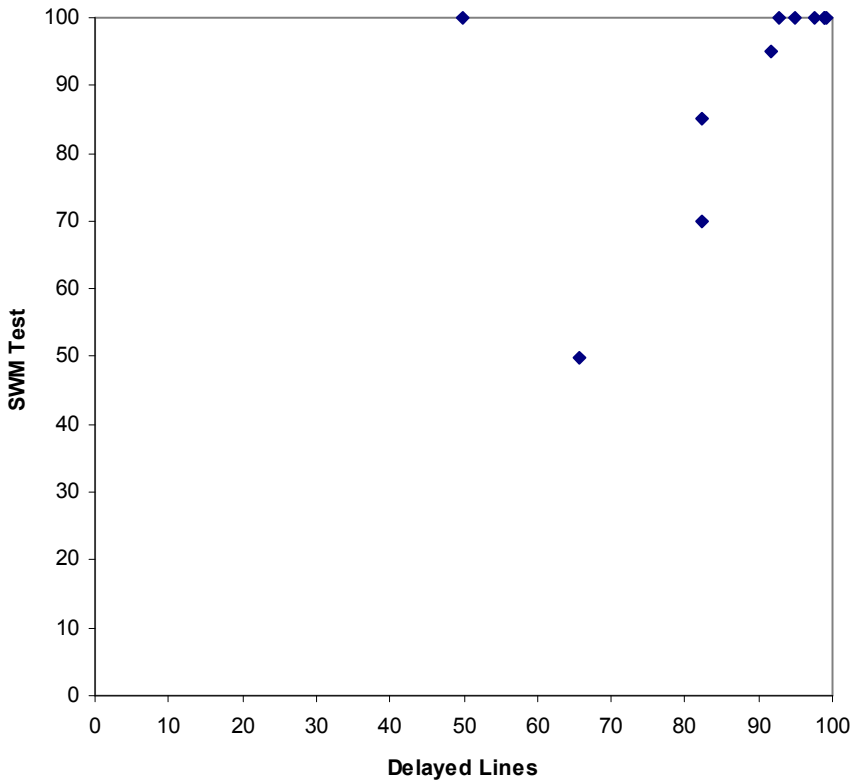


Fig.3.3: Scatter plot of the correlation between the mean percentage of correct delayed lines (left, centre and right targets taken together) and percentage of correct SWM trials (1st block) for the N+ and N- patients.

3.2.2.1. Percentage of correct saccades within 60 degrees

A saccade was rated as correct if it ended within a cone of 30 degrees to either side of the line (fig. 3.4) (adapted from Butler et al., 2006).

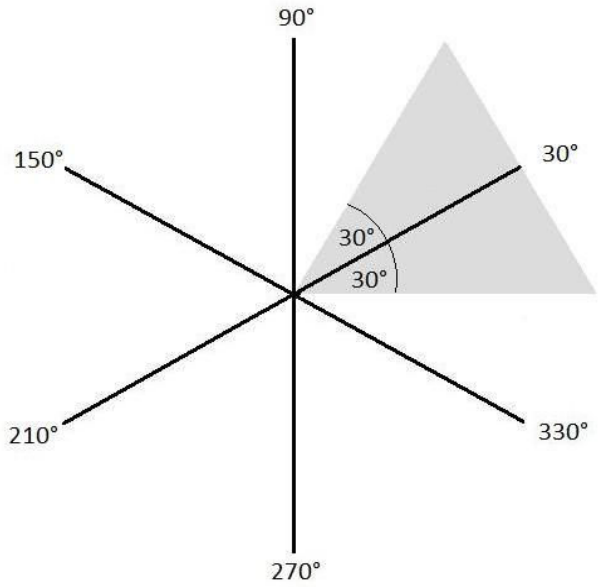


Fig 3.4: Schematic layout of the possible six line locations and the 60 degrees cone around a line, in which the saccade had to end to be identified as correct.

In the stimulus-driven, immediate saccade condition, the healthy controls performed perfectly with 99.6% (SD 1.4) correct trials for left lines, 98.3% (SD 2.5) correct trials for central lines and 98.2% (SD 1.9) correct trials for lines pointing to the right side. Proportions in the memory-guided, delayed saccade condition were slightly lower with 98.3% (SD 2.8) for left lines, 96.2% (SD 5.4) for central lines and 96.9% (SD 3.2) for right lines. The N+ patient group showed fewer correct saccades with 90.2% (SD 11.7) for left, 88% (SD 6.1) for centre and 93.8% (SD 9.1) for right stimulus-driven saccades, and 87.5% (SD 12.3) for left, 72.8% (SD 23.6) for centre and 75% (SD 35.5) for right memory-guided saccades. The results for the N- group were 98.9% (SD 2.74), 96.6% (SD 3.9) and 93.4% (SD 9.2) for left, centre and right

immediate saccades and 95.1% (SD 4.8), 94.2% (SD 7.3) and 91.8% (SD 8.8) for left, centre and right delayed saccades (see also table 3.4).

A 3x2x3 mixed ANOVA with the independent variables *group* (controls, N+, N-) as a between-subject factor and *condition* (stimulus driven, memory guided saccades) and *side* (left, centre, right targets) as the within-subject factor revealed main effects of *group* [$F_{(2,20)}$=7.3, p<.01] and *condition* [$F_{(1,20)}$=11.2, p<.01]. This was qualified by a significant interaction of *group x condition* [$F_{(2,20)}$=3.6, p<.05] (table 3.3).

Table 3.3: ANOVA with the factors side, condition and group for percentage of correct saccades within 60 degrees. Significant main effects and/or interactions in italic.

		df	F	Sig.
Within-Subjects Effect	***Condition***	*1*	*11.162*	*.003*
	Condition x Group	*2*	*3.625*	*.045*
	Error (Condition)	20		
	Side	*2*	*3.421*	*.043*
	Side x Group	4	1.245	.308
	Error (Side)	40		
	Condition x Side	2	1.492	.237
	Condition x Side x Group	4	1.594	.195
	Error (Condition x Side)	40		
Between-Subjects Effect	***Group***	*2*	*7.313*	*.004*
	Error	20		

Looking at the interaction of *group x condition*, pairwise comparisons revealed that controls differed significantly from the N+ group for the delayed condition (p<.01) with the N+ patients being more impaired (mean difference between the groups 18.7%). Also, the N+ patients performed significantly worse than the controls in the immediate condition, although this difference was much smaller (p<.01; mean difference between the groups 8.3%). There was no significant difference between the N- group and any other group (fig. 3.5 and 3.6).

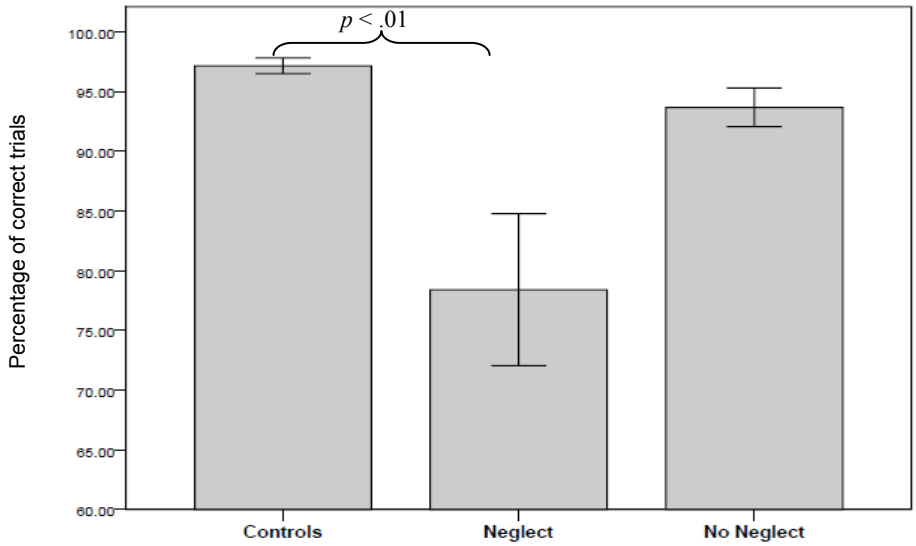


Fig 3.5: Mean percentage of correct trials for the delayed lines condition for the control, neglect (N+) and no neglect (N-) groups. Error bars show +/- 1 SE.

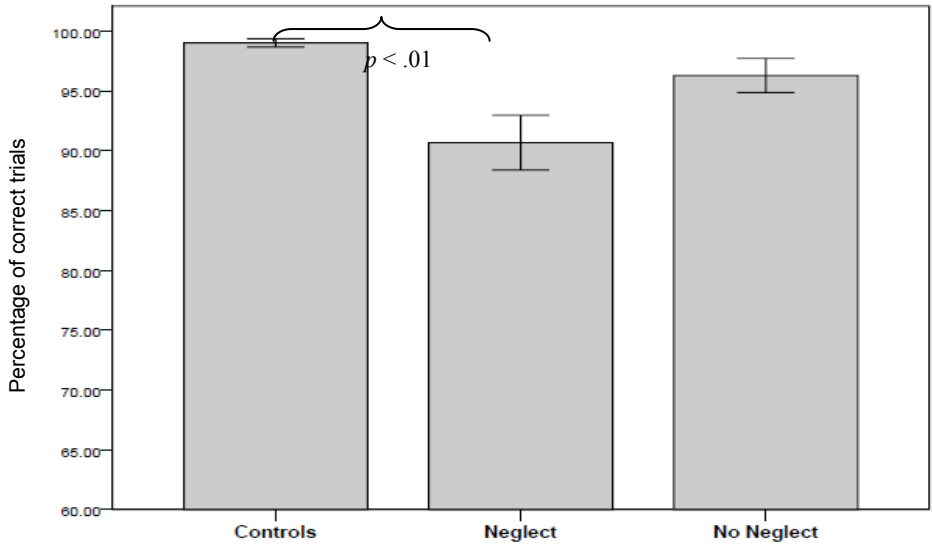


Fig 3.6: Mean percentage of correct trials for the immediate lines condition for the control, neglect (N+) and no neglect (N-) groups. Error bars show +/- 1 SE.

On an individual level three neglect patients were significantly impaired for both conditions and for most of the line directions. JK (fronto-temporal lesion) showed a severe overall deficit compared to the control group (left, centre and right immediate and delayed lines: each $p<.001$). Furthermore, JH (fronto-temporo-parietal lesion) only showed no impairment for right immediate lines (all other trials were clearly impaired:

p<.001) and PI (fronto-temporo-parietal lesion) was able to execute left and right memory-guided saccades (all other trials were clearly impaired: p<.001). While for the N+ patients an overall deficit was found, the N- patients on the other hand were not generally impaired but simply for selected line directions and/or conditions. For example JG was only impaired for left delayed lines (p<.01), DG for left immediate lines (p<.001) and AM and JC for right immediate lines (both p<.001). Only WG (fronto-temporal and subcortical lesion) showed a clear tendency to be more impaired for delayed lines (left and centre: p<.05, right: p<.001) than for immediate lines where he was only slightly impaired for right target lines (p<.05). All Crawford and Howell (1998) test results can be found in table 3.4.

Table 3.4: Percentage of correct saccades towards a line for the immediate lines condition and the delayed lines conditions; left, centre and right targets; group data and individual scores. Significance level for Crawford & Howell's modified t-test (two-tailed): ***=p<.001, **=p<.01, *=p<.05.

		immediate, stimulus-driven saccades			**delayed, memory-guided saccades**		
		Left	**Centre**	**Right**	**Left**	**Centre**	**Right**
Controls		99.6 (SD 1.4)	98.3 (SD 2.5)	99.2 (SD 1.9)	98.3 (SD 2.8)	96.2 (SD 5.4)	96.9 (SD 3.2)
N+		90.2 (SD 11.7)	88 (SD 6.1)	93.8 (SD 9.1)	87.5 (SD 12.4)	72.8 (SD 23.7)	75 (SD 35.5)
N-		98.9 (SD 2.7)	96.6 (SD 3.9)	93.4 (SD 9.2)	95.1 (SD 4.8)	94.2 (SD 7.3)	91.8 (SD 8.8)
N+	**PI**	90.9***	83.3***	88.9***	100	53.8***	93.3
	MM	100	94.4	100	90.9*	96.7	97.1
	JK	71.4***	83.3***	80***	72.7***	61.5***	15.4***
	JH	88.9***	84.2***	100	76.2***	51.9***	69.2***
	AK	100	95	100	97.5	100	100
N-	**JG**	100	100	100	88.9**	96.4	93.3
	DG	93.3***	94.4	100	93.1	91.3	90.5
	WG	100	94.4	94.7*	90.9*	80.8*	75***
	JS	100	100	100	100	100	96.7
	AM	100	100	88.2***	100	96.7	100
	JC	100	90.9*	77.3***	97.4	100	95.1

Next, the mean scores for memory-guided trials for each participant were subtracted from those obtained from the stimulus-driven saccade trials to investigate the size of the difference between these two conditions. This calculation could result in a positive or negative difference. A positive sign indicated that the participant performed worse in the memory-guided condition, with a negative sign indicating a better performance on memory-guided trials indicated compared to the stimulus-driven condition.

Control participants showed small positive differences between the two conditions [1.3% (SD 3.4), 2.1% (SD 6) and 2.2% (SD 3.8) for left, centre and right stimuli] indicating that their performance on stimulus-driven saccades was just slightly better.

Contrary, the group of N+ patients showed only for left targets a small positive difference score, while the difference between the conditions was much bigger for central and right targets [2.8% (SD 8.6), 15.3% (SD 17.7) and 18.8% (SD 29.1) for left, centre and right stimuli]. These results indicated that they performed much better in the stimulus-driven condition than in the memory-guided condition for central and right targets, while for left targets the increase of correct saccades in the stimulus-driven conditions was only minimal compared to the other condition. The performance of the N- group was similar to the healthy control participants with a small difference between the two conditions [3.8% (SD 5), 2.4% (SD 7.3) and 1.6% (SD 14) for left, centre and right stimuli] (see also table 3.6).

A 3x3 mixed ANOVA with *group* as the between-subject factor and *side* as the within-subject factor revealed a main effect of *group* [$F_{(2,20)}=3.6$, $p<.05$] (table 3.5).

Table 3.5: ANOVA with the factors side and group for mean difference between both conditions in percentage. Significant main effects and/or interaction in italic.

		df	F	Sig.
Within-Subjects Effect	**Side**	2	1.489	.238
	Side x Group	4	1.594	.195
	Error (Side)	40		
Between-Subjects Effect	***Group***	*2*	*3.628*	*.045*
	Error	20		

A pairwise comparison showed a significantly greater difference between both conditions for the N+ group compared to the healthy controls (p<.05). No significance was found for any other comparison (fig. 3.7).

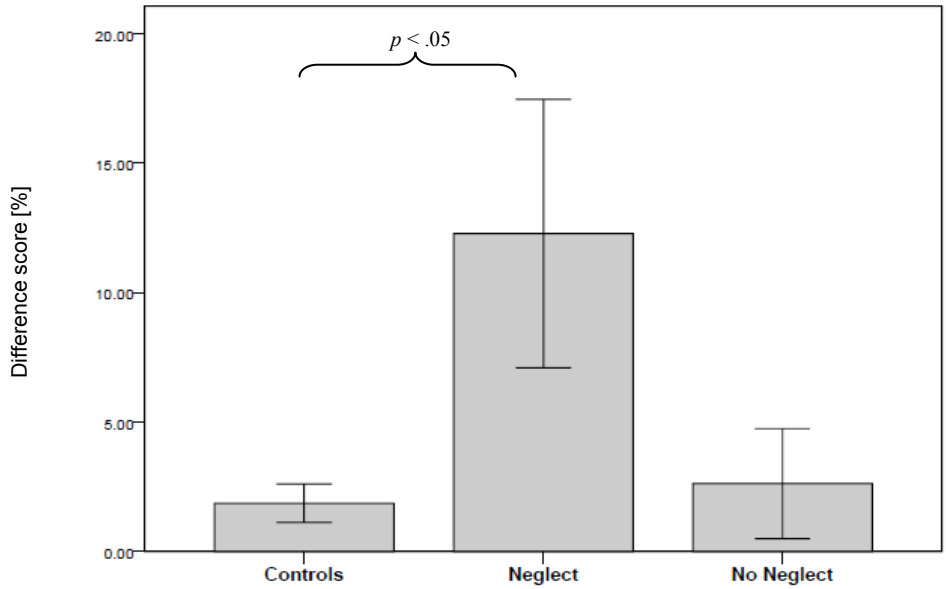


Fig 3.7: Mean difference between both conditions in percentage for the control, neglect (N+) and no neglect (N-) groups. Error bars show +/- 1 SE.

On an individual level, neglect patient JH (fronto-temporo-parietal lesion) showed an overall worse performance compared to the healthy control group. This can be seen in her high positive difference score which indicates fewer correct memory-

guided saccades than immediate saccades for all target line directions (left: $p<.01$; centre and right: $p<.001$). Likewise, N+ patients PI, MM and JK show significantly greater positive difference scores compared to the controls (PI: centre $p<.001$; MM: left $p<.05$; JK: centre $p<.05$, right $p<.001$). For the N- group, only JG and WG differed from the controls (JG: left $p<.05$; WG: left $p<.05$, right $p<.001$). However, while most participants executed fewer correct memory-guided saccades than stimulus-driven saccades, resulting in a positive difference score, it also occurred that participants performed better for the delayed conditions. This resulted in a negative difference score. Patient PI's performance resulted in a greater negative difference score for left targets compared to the controls ($p<.05$) and likewise the negative difference scores for right targets of N- patients AM and JC differed significantly from the controls (AM $p<.01$; $p<.001$). All Crawford and Howell (1998) test results can be found in table 3.6.

Table 3.6: Difference in percentage between the two experimental conditions (calculated as percentage of correct delayed saccades minus percentage of correct immediate saccades) for left, centre and right targets; group data and individual scores.
Significance level for Crawford & Howell's modified t-test (two-tailed): ***=$p<.001$, **=$p<.01$, *=$p<.05$.

		difference between conditions		
		Left	**Centre**	**Right**
Controls		1.3 (SD 3.4)	2.1 (SD 6)	2.2 (SD 3.8)
N+		2.8 (SD 8.6)	15.3 (SD 17.7)	18.8 (SD 29.1)
N-		3.8 (SD 5)	2.4 (SD 7.3)	1.6 (SD 14)
N+	**PI**	-9.1*	29.5***	-4.4
	MM	9.1*	-2.3	2.9
	JK	-1.3	21.3*	64.6***
	JH	12.7**	32.3***	30.8***
	AK	2.5	-5	0
N-	**JG**	11.1*	3.6	6.7
	DG	0.2	3.1	9.5
	WG	9.1*	13.6	19.7***
	JS	0	0	3.3
	AM	0	3.3	-11.8**
	JC	2.6	-9.1	-17.8***

3.2.2.2. Saccadic Reaction Time of first saccade

All three subject groups showed longer latencies for memory-guided saccades compared to stimulus-driven saccades, regardless of the direction in which the target line pointed. For lines pointing to the left side, healthy participants had a mean reaction time of 471 ms (SD 38.9) for the memory-guided condition while their reaction time for the stimulus-driven condition was faster with 320 ms (SD 50.3). For the N+ patients these reaction times were 522 ms (SD 186.9) and 330 ms (SD 114.9) respectively, and for the N- patients these reaction times were 459 ms (SD 62.9) and 341 ms (SD 57.8). Similar reaction times were found for central target lines with 456 ms (SD 69) for memory-guided saccades and 309 ms (SD 32.3) for stimulus-driven saccades for healthy controls. N+ patients showed mean reaction times of 538 ms (SD 117.1) and 341 ms (SD 86.2) for memory-guided and stimulus-driven saccades towards central targets. The N- patient group had a mean reaction time of 471 ms (SD 72.2) for the memory-guided saccade condition and 359 ms (SD 73.7) for the stimulus-driven saccade condition.

For right targets the reaction times were as follows: 437 ms (SD 53) and 294 ms (SD 42) for memory-guided and stimulus-driven saccades for healthy controls, 520 ms (SD 171.1) and 346 ms (SD 102) for the group of N+ patients, and 482 ms (SD 72.2) and 337 ms (SD 75.9) for memory-guided and stimulus-driven saccades to right targets for the N- patient group (see also table 3.8).

A 3x2x3 mixed ANOVA with *group* (control, N+, N-) as the between-subject factor and *condition* (stimulus-driven, memory-guided saccades) and *side* (left, centre, right targets) as the within-subject factor revealed a main effect of *condition* [$F_{(1,20)}$=69.9, p<.001] only with an overall slower performance in the memory-guided condition compared to the stimulus-driven condition (table 3.7; fig. 3.8). As the assumption of sphericity had not been met for the interaction of *side x condition*

(Mauchly's W=.703, p<.05), the Greenhouse-Geisser correction was used for the factor side.

Table 3.7: ANOVA with the factors side, condition and group for the SRT of correct saccades. Significant main effects and/or interactions in italic; * = Greenhouse-Geisser correction for df.

		df	F	Sig.
Within-Subjects Effect	**Condition**	1	69.863	<.001
	Condition x Group	2	.812	.458
	Error (Condition)	20		
	Side	2	.492	.615
	Side x Group	4	1.088	.375
	Error (Side)	40		
	Condition x Side	1.543*	.005	.995
	Condition x Side x Group	3.085*	.340	.849
	Error (Condition x Side)	30.851*		
Between-Subjects Effect	**Group**	2	1.6	.227
	Error	20		

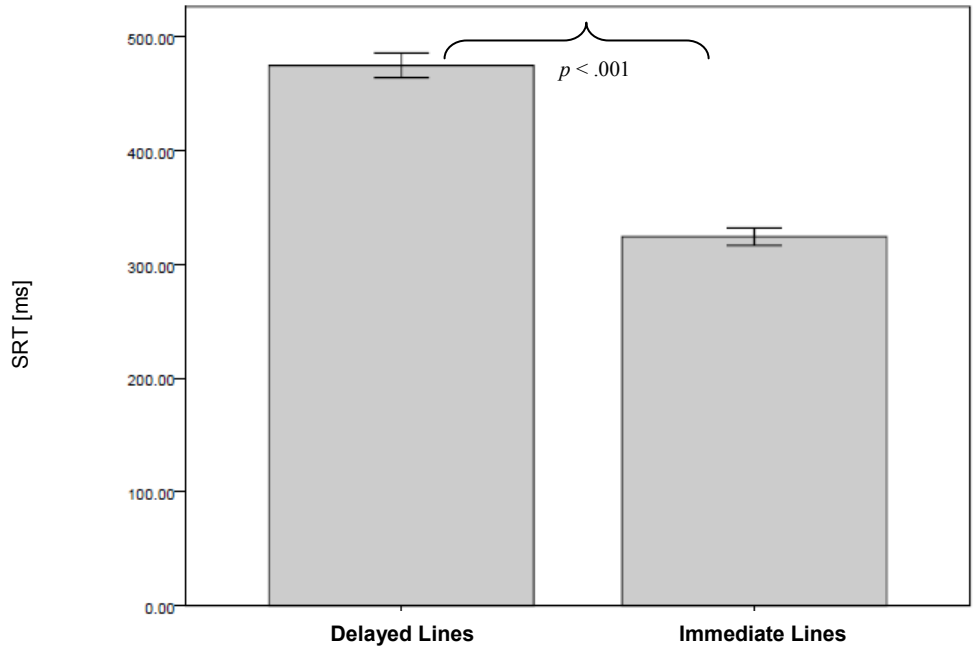


Fig 3.8: Overall mean Saccadic Reaction Time of correct trials for the delayed line condition and the immediate line condition. Error bars show +/- 1 standard error.

On an individual level the majority of the patients showed no increased latencies for all or for selected directions. However, neglect patients JH and AK showed significantly longer reaction times compared to the healthy controls with the only exemption being delayed saccades to the left for JH and to the centre for AK. Here AK and JH did not differ from the healthy controls. Further impairments were found for N+ patient PI, who needed longer to respond to left (p<.001) and to centre delayed targets (p<.05). For no-neglect patients only JS and AM showed significant longer latencies to selected target directions. JS was impaired for right delayed targets (p<.01) and AM responded slower to centre and right immediate lines (both p<.001). Please see table 3.8 for detailed information.

Table 3.8: SRT in ms of correct saccades towards a line for the immediate lines condition and the delayed lines conditions; left, centre and right targets; group data and individual scores. Significance level for Crawford & Howell's modified t-test (two-tailed): ***=p<.001, **=p<.01, *=p<.05.

		immediate, stimulus-driven saccades			delayed, memory-guided saccades		
		Left	**Centre**	**Right**	**Left**	**Centre**	**Right**
Controls		320 (SD 50.3)	309 (SD 32.3)	294 (SD 42)	471 (SD 38.9)	456 (SD 69)	437 (SD 53)
N+		330 (SD 114.9)	341 (SD 86.2)	346 (SD 102)	522 (SD 187)	538 (SD 117)	520 (SD 171.1)
N-		341 (SD 57.8)	359 (SD 73.7)	337 (SD 75.9)	459 (SD 62.9)	471 (SD 72.2)	482 (SD 72.2)
N+	**PI**	327	263	327	796***	617*	509
	MM	212	243	210	316	370	383
	JK	220	362	300	399	463	325
	JH	450*	392*	466**	496	641*	716***
	AK	440*	446**	426*	602**	602	668**
N-	**JG**	293	328	259	438	551	508
	DG	367	313	305	357	426	447
	WG	255	325	307	443	494	467
	JS	343	299	316	528	562	609**
	AM	412	492***	478***	521	392	464
	JC	377	400*	356	468	403	396

3.2.3. Discussion

My results show that delayed and immediate responses differed significantly from each other with regard to reaction time and proportion of correct saccades. I found overall longer latencies and greater errors, i.e. a greater number of the saccades that ended outside the 60 degree cone, for the delayed lines condition. Although no significant latency differences were found between the three participant groups I tested, the N+ group was clearly impaired overall with regard to saccade accuracy. On the other hand, N- stroke patients did not perform significantly different from the healthy controls. However, as I did not find any difference between the N+ and N- group either, my data lead to the assumption that the observed impairment may not be neglect specific.

Although Butler et al. (2009) reported that neglect patients were impaired on stimulus-driven pro-saccades towards left sided targets and other studies found that neglect patients failed to respond to contralesional targets at all (Duhamel et al., 1992; Niemeier & Karnath, 2003), I found no difference between left, centre and right targets. This could be the result of the fact, that most of the patients did not show acute neglect and had recovered already. Alternatively, although the neglect patients in Butler et al.'s study never failed to make an eye movement towards left targets their saccades showed great inaccuracy. While Butler and colleagues calculated the accuracy as the difference between the saccade landing point and the target location, I defined a response as correct when the saccade landing point was within a 60 degree cone around the target line. Thus I cannot say how close the saccade was to the actual line, but for me it was more important to find out if the line direction was perceived and remembered correctly. This display was chosen out of consideration for the capabilities of the elderly controls and patients but also to make the delay condition feasible for comparison with the agnosia patient DF (see 3.2, first paragraph).

Brain Areas implicated in memory- guided saccades

Regarding the conditions and as predicted, I found that N+ patients were most impaired in the memory-guided saccades. They showed a clear decrease of correct responses for delayed compared to immediate lines, which was reflected in a high difference score between the two conditions. This impairment for delayed lines seems to be the result of impairment in general memory-guided saccades, in line with my initial predictions, extending Rossit et al's (2009b) findings into the oculomotor domain. They observed that hemispatial neglect patients were specifically impaired in the accuracy of their leftward delayed pointing and that these deficits were associated with lesions to temporal areas. In line with this, the four most impaired stroke patients (JH, JK, PI, and WG) in my study all had temporal lobe lesions, giving further evidence for these areas to be implicated in delay. Nonetheless it has to be granted that unlike the Rossit et al. data; my results were neither specific to the left, nor neglect specific although 3 out of the 4 most impaired patients showed neglect symptoms.

Milner and Goodale (e.g. 1995, 2006) proposed that areas outside the PPC may be involved in delayed responses. So far the evidence for this comes largely from reaching and grasping studies, but my data give some support for this idea from the oculomotor domain. Nonetheless as covered in the introduction to this chapter, the PPC and the IPS in particular have also been implicated in memory-guided saccades (Müri et al., 1996; Nyffeler et al., 2005). In fact one of the most impaired patients, who showed the greatest performance decrease from the immediate to the delayed task, had a lesion involving the parietal lobe (patient JH), which very likely involved the IPS. Another neglect patient who, according to his lesion (fronto-temporo-parietal) might also possibly have a damaged IPS is PI. However, his results are based on very few trials only, because of insufficient fixation at the beginning of most trials; therefore I will not make any further assumptions based on his results. Further patients with parietal and

thus potential IPS lobe damage are N+ patients MM and AK and N- patient JS who show no or very small differences between the two tasks. I may thus cautiously argue that the parietal lobe may be less implicated in impairments in memory-guided saccades than the temporal lobe.

A further look at the lesions indicates a possible involvement of frontal areas in the performance of delayed lines. Four of my neglect patients (PI, MM, JK, and JH) and three no-neglect patients (WG, JS, JC) had lesions to the frontal lobe and four of these patients performed worse in the delayed condition. In line with these findings, Hanes, Patterson and Schall (1998) found evidence for neurons with eye movement related activity in the FEF of monkeys that increased their activity during the preparation of a saccade. Also, FEF activity during a delayed saccade task has been reported previously (Connolly et al., 2002; Curtis & D'Esposito, 2006) and the authors suggested that the FEF is involved in conducting an eye movement once the target location is selected. In a similar fashion I could argue that the saccade accuracy failure might occur because of the frontal lobe lesions as the target location in my task was known during the delayed interval and with that, the direction in which the saccade had to be made was already selected. What goes against this argument is the finding that neglect patient MM and no neglect patient JS performed almost perfectly despite dorsal frontal lobe lesions that most likely included the FEF.

Finally, patient WG, who performed very poorly in the delayed lines condition while he was not impaired in the immediate line condition, also suffers from a lesion to the basal ganglia and the contribution of the basal ganglia to saccadic eye movements has been reported previously (Hikosaka, Takikawa & Kawagoe, 2000; Ford & Everling, 2009). Moreover, it was found in primates that the basal ganglia project to the frontal lobe (Wise, Murray & Gerfen, 1996), an area that is also damaged in WG.

Other potential contributors driving differences in task performance

Apart from particular brain lesions, there might be other factors that could have interfered with the performance of the participants. These will be discussed in the following.

Although five of my eleven stroke patients (two N+ and three N- patients) suffered from visual field deficits, in particular to the left side, it is very unclear how much this contributed to the impairments in the experimental task. All N- patients responded well towards immediate left targets. However, as both neglect patients with visual field deficits were impaired for most of the immediate trials, particularly for left trials, it cannot be said for sure if this is the result of the hemianopia or typical neglect behaviour with omissions to the left side.

I also looked at chronicity but did not find any links to impairments in the task. Patients PI and WG, whose time since injury onset was only five and three month respectively, showed deficits in the delayed task, but patients JK and JH, who were tested 38 and 43 months respectively after injury onset, were also seriously impaired.

Furthermore, as the delayed condition of the experiment required the memorisation of a line, spatial working memory, as tested prior to the experimental task, might be crucial. Indeed, a correlation was found between a low score in the SWM test (Malhotra et al., 2005) and impairment in the delayed line condition. This result could indicate that the participants who failed in the memory-guided task may have a general memory deficit, which would affect the performance. In fact two out of three patients (PI and WG) who performed worst on the SWM test were significantly more impaired in the delay task.

Finally the task itself could have contributed to a greater failure in the delayed line condition compared to the immediate line condition. The line that the participants were required to memorise was presented for 200 ms only before it disappeared again,

while it was presented for 1,000 ms in the immediate condition. One could argue that the perception of a line for 1,000 ms vs. 200 ms is not comparable and therefore triggers different processes, and I have to acknowledge that this design was not ideal. However, the participants were not intended to wait the whole 1,000 ms before initiating a response and indeed mean saccadic reaction times for immediate lines were much smaller (mean saccadic reaction time across all directions were 319 ms for the controls, 339 ms for the N+ group and 346 ms for the N- group). Also, the short presentation duration of the line in the delayed condition was chosen to prevent the participants from making a stimulus-driven saccade to the line when it was still present, as that could have made it easier for them to remember the location later. It would be worthwhile to follow this study up with a design that focuses on delayed conditions in particular. While this would not allow an examination of immediate saccades, it would allow a fairer balance of stimuli.

Furthermore, it has to be acknowledged that the current design introduced a difference in the stimuli presentation, i.e. the stimulus was present when a saccade was made in one condition (immediate) but not in the other condition (delayed). It would be interesting to follow this study up with a design that would allow a comparison of findings observed here, with one where a visual stimulus was present in both conditions at the time of saccade onset.

To summarise my findings, neglect patients showed a clear impairment to perform delayed saccades to left, centre and right target lines compared to healthy controls but there was no difference in their performance in relation to the no-neglect group. These results can extend Rossit et al.'s (2009b) findings to the oculomotor domain although I failed to find a specific neglect or left delay impairment. However in line with my findings, Butler et al., (2009) also reported that neglect patients were severely impaired in the execution of anti-saccades, i.e. off-line performance, to both

left and right stimuli (see also chapter 2) and more recently Rossit et al. (2011) also found bilateral anti-pointing impairments in a group of neglect patients, so the lack of laterality differences in my findings seems in line with some other neglect studies.

Also, the N+ group, like the healthy controls and the N- group, performed better for the immediate lines than for delayed lines and on a group level no difference was found between the groups for the immediate, on-line condition. However, on an individual level some of the patients were significantly impaired for the immediate condition. Unfortunately, I cannot give any specific conclusions regarding brain areas, as the patients I tested varied greatly. Nevertheless, from a behavioural point, the patients performed as expected, with greater problems for memory-guided lines, i.e. for the off-line task.

3.3. Experiment 4: On-line correction

I have previously shown (chapter 3.2) that the group of neglect patients I tested was impaired in delayed, off-line saccades compared to the healthy controls. On the other hand no difference between these two groups was found for the immediate, on-line condition.

As described under 3.1.3 various studies have found evidence that the PPC, which is believed to be involved in dorsal stream activity, plays a role in on-line control (e.g. Grea et al., 2002). While healthy participants adjust their response automatically towards a target that sudden changes its location (Pisella et al., 2000), other results show that optic ataxia patients who frequently have a lesion to the PPC, fail to adjust their movement towards a perturbed target as quickly as healthy participants (e.g. Grea et al., 2002; Blangero et al., 2008). Furthermore it has also been found, that optic ataxia patients, whose ventral stream is usually spared, improve their performance in delayed, memory-guided off-line tasks (Milner et al., 1999; Milner et al., 2001).

As patients with hemispatial neglect seem to be able to perform simple on-line tasks like pro-pointing or pro-saccades, this second experiment was now conducted to further test these on-line performances and particularly oculomotor on-line corrections to perturbed targets. For my task I modified the experimental setting of Pisella et al. (2000), Blangero et al. (2008) and Rossit and Harvey (2008). While they tested the pointing performance of healthy participants and optic ataxia patients, I aimed to examine stroke patients with and without hemispatial neglect (for patient DF please see chapter 5) with an oculomotor task that required eye movements to stationary targets and to perturbed targets. Like Rossit and Harvey (2008), 30% of my targets will suddenly change location and 70% of the trials will be stationary (see also Gaveau et al., 2008 who tested both manual and ocuolomotor on-line corrections).

As neglect frequently occurs after lesions to either the right IPL (Mort et al., 2003) or the superior temporal lobe (Karnath, Ferber & Himmelbach, 2001; Karnath et al., 2004), with a spared dorsal stream (Milner & Goodale, 1995), I predict that the neglect patients will show no deficits in this on-line task. I expect them to saccade towards the stationary targets as well as towards the perturbed targets as accurately and fast as the healthy controls. Furthermore I expect any failure to be linked to PPC lesions. These predictions are also in line with previous behavioural findings of neglect patients being able to perform on-line oculomotor tasks and showing deficits for off-line oculomotor tasks (see chapter 2 and 3.2). They are further supported by previous studies that have tested direct pointing or grasping (on-line) behaviour in these patients (e.g. Himmelbach & Karnath, 2003; Rossit et al., 2009b).

3.3.1. Method

Healthy participants

The same 12 healthy elderly right-handed subjects (mean age 66.4 years, SD 8.5) as in the previous study (chapter 4) participated in this study.

Patients

Eleven right hemisphere stroke patients took part in the study, ten of which also participated in the previous experiment (chapter 3). N- Patient JG did not participate again; instead I recruited RM, who also had never suffered from neglect.

Prior to taking part in my experiment, all patients were tested with the *Behavioural Inattention Test* (BIT, Wilson, Cockburn and Halligan, 1987), *Line Bisection* (Harvey, Milner and Roberts, 1995) and the *Balloons Test* (Edgeworth, Robertson and McMillan, 1998). This resulted in five N+ and six N- patients. Furthermore, I tested for visual field deficits and extinction with laptop based tests. Four of my eleven patients showed a visual field deficit with three patients having a hemianopia for the left visual field and one patient showing a lower left quadrantanopia. Furthermore, two patients showed extinction. For a description of the subject group classification and the tests that were conducted for assessment please see chapter 2.2. Please see table 3.9 (a) and (b) for demographic and clinical details and fig. 3.9 for lesion locations.

Patients were recruited from the Southern General Hospital in Glasgow. The study was conducted in accordance with the ethical guidelines of the South Glasgow University Hospitals NHS Trust and the Declaration of Helsinki. All participants gave their informed consent prior to the study.

Table 3.9 (a): Demographic and clinical data of right hemisphere stroke patients. Initials of patients who took part in the memory guided-saccade study (chapter 3.2) are written italic, and in bold and italic when patient had taken part also in the fixation and memory-guided study (chapter 2.3 and 3.3).

PATIENT	GENDER	AGE	SCAN	ETIOLOGY	LESION LOCATION	VISUAL FIELD DEFICIT	EXTINCTION
PI	M	56	MRI	Infarct	fronto-temporo-parietal	YES	YES
MM	F	66	MRI	Infarct	dorsal frontal, parietal, corona radiata	NO	NO
JK	F	72	CT	Infarct	fronto-temporal	NO	NO
JH	F	58	MRI	Infarct	fronto-temporo-parietal	YES	YES
AK	F	69	CT	Infarct	posterior frontal, posterior insular, parietal	NO	NO
RM	M	75	CT	Infarct	posterior limbic system, internal capsule	NO	NO
DG	M	60	CT	Infarct	Right MCA, temporal + insular cortex, posterior lentiform nucleus	NO	NO
WG	M	67	MRI	Infarct	Right MCA, basal ganglia and pallidus, temporal + frontal cortex	YES	NO
JS	M	56	CT	Infarct	dorsal frontal, posterior temporal, parietal	YES	NO
AM	M	63	CT	Infarct	lentiform nucleus	NO	NO
JC	M	76	CT	Ischemia	Right MCA, frontal lobe, anterior insula cortex	NO	NO

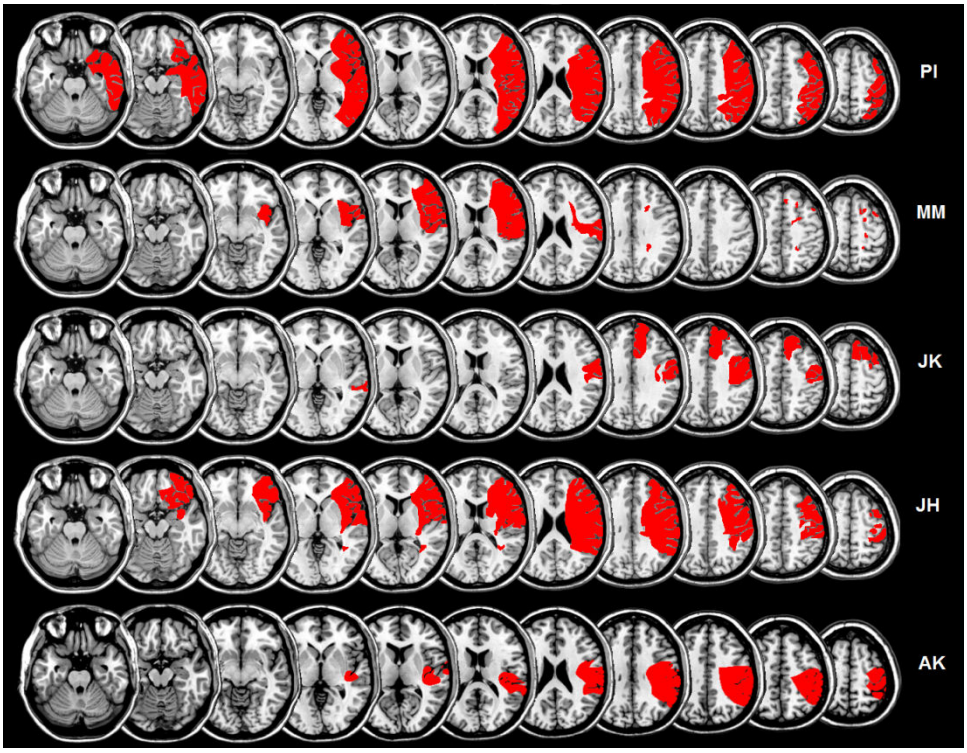
Table 3.9 (b): Clinical data of right hemisphere stroke patients. Initials of patients who took part in the memory-guided saccade study (chapter 3.2) are written italic, and in bold and italic when patient had taken part also in the fixation and memory-guided study (chapter 2.3 and 3.2).

PATIENT	TIME SINCE INJURY ONSET 1	LINE BISECTION	BALLOONS	BIT 1	TIME SINCE INJURY ONSET 2	BIT 2	GROUP
PI	5	50	11%	84	-	-	N+
MM	2	3	59%	142	31	144	N+
JK	4	15	44%	141	38	135	N+
JH	10	14	50%	132	43	139	N+
AK	1	16	43%	121	25	142	N+
RM	30	6	46%	141	-	-	N-
DG	3	3.7	50%	144	-	-	N-
WG	3	5.6	50%	143	-	-	N-
JS	14	1	53%	146	-	-	N-
AM	40	3	50%	146	-	-	N-
JC	3	4.8	47%	138	-	-	N-

BIT = Behavioural Inattention Test (cut-off score 129), Line Bisection cut-off score 6; Balloons cut-off score 45%,
Time Since Injury Onset 1 = time (in months) elapsed when assessed for the first time, but if time between assessment and participating in experiment was too long, patients were retested with the BIT (BIT2), Time Since Injury Onset 2 = time (in months) elapsed when retested; N+ = neglect group, N- = no neglect group

Lesion locations

(a)



(b)

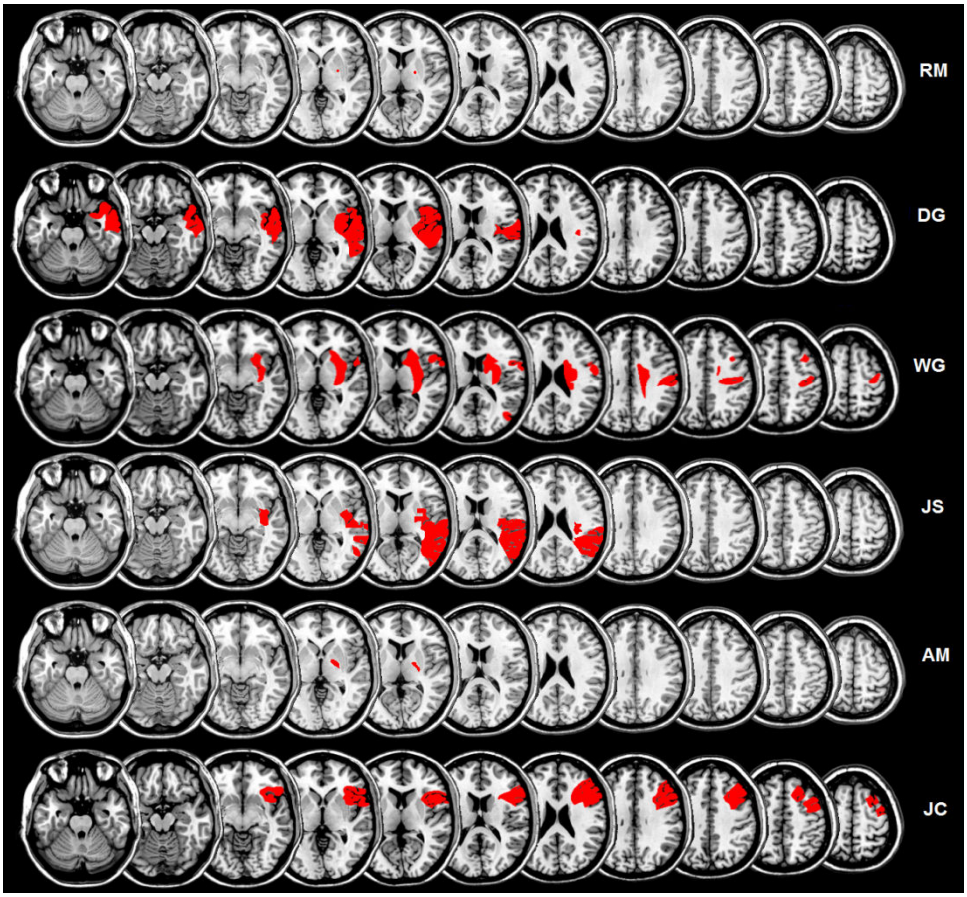


Fig. 3.9: Voxel-based lesion maps for each patient with hemispatial neglect (a) and without hemispatial neglect (b) in axial view.

Apparatus and stimuli

A white circle with a diameter of 0.7 degrees was displayed centrally at the bottom of the screen (located at position 400 x 500 pixel) and served as a fixation point. A white circle of the same size served as a target stimulus and was presented at the top of the screen (position 400 x 100 pixel). This was the target location for no-jump trials. For jump trials an invisible boundary was drawn at 1 degree around the fixation dot. Whenever a saccade outside this boundary was identified, the top central target dot was triggered to jump 2 degrees either to the left (position 348 x 100 pixel) or the right (position 452 x 100 pixel) side. The equipment for stimuli presentation and recording was similar to the previous experiment (see chapter 2 and 3.2).

Procedure

The experimental task consisted of three blocks with 60 trials each (42 no-jump trials, 9 trials in which the dot jumped to the left side, and 9 trials in which it jumped to the right side). At the beginning of the experiment, the task was explained with the help of 12 practice trials, which could be repeated if necessary until the subject had understood the task although this proved not the case for any of the participants. Each of the three blocks of trials started with a nine-point grid calibration and validation procedure (for details please see chapter 2.2).

For each trial, participants were instructed to fixate the central circle. The actual task was manually started by the experimenter via button press. In the no-jump trials the target dot appeared in the centre at the top of the screen and a saccade was required towards it as quickly and accurately as possible. In the jump trials the dot appeared in the same position as in no-jump trials but as soon as the participant saccaded towards it a jump of that central dot either to the left or the right side was triggered. Again, the subject had to look at the dot and had to follow it to the new location. After that, the

fixation and the target dot disappeared together and the screen went blank for another 1,000 ms until a new fixation point appeared. Each participant had to complete all three blocks and the trial order was random. Example displays are shown in figure 3.10.

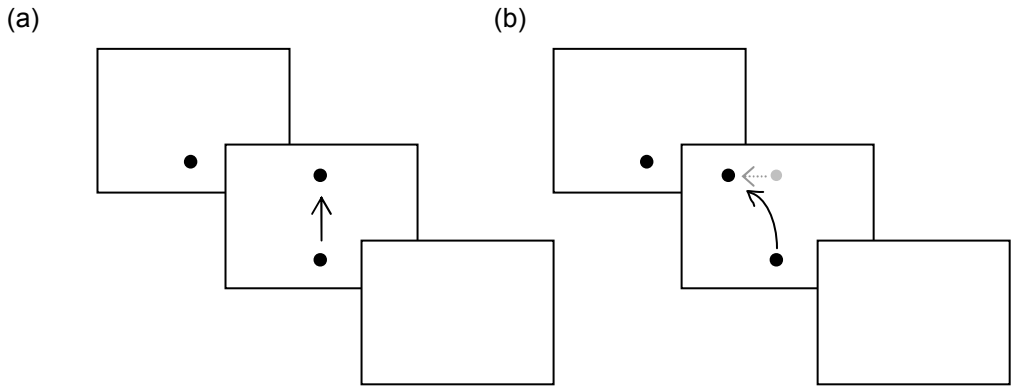


Fig. 3.10: Schematic layout of the no-jump and the jump conditions. In the no-jump condition (a), the participant was required to initiate a saccade towards the target dot as quickly and as accurately as possible. In the jump condition (b), the target dot "jumped" to the left or right side as soon as the participant initiated a saccade. Again, the participant was required to follow the target to its new location.

Data processing

Trials in which a first saccade after stimulus onset was made with a latency shorter than 80 ms were considered anticipatory and were excluded from further analysis. Also, trials in which the central circle was not properly fixated after stimulus onset (deviation larger than 2 degrees) were excluded from analysis. Finally trials in which the first saccade was too small (shorter than 1 degrees) were also excluded.

These criteria resulted in a rejection of 20.4% for the no-jump trials for the healthy controls, 39.8% for the stroke patients with neglect (N+), and 30.3% for the stroke patients without neglect (N-). For the jump trials, these numbers were 20.2%, 31.5% and 30.6% respectively. Please see table 3.10 for more details regarding the number of excluded trials for each criterion.

Table 3.10: Percentage of excluded trials for the anticipation, fixation and amplitude criteria, for no-jump and jump trials, presented separately for healthy controls, N+ and N- patients.

		No-Jump	Jump
Controls	**Anticipation**	7.4%	6.3%
	Fixation	10.7%	9.9%
	Amplitude	2.3%	4%
N+	**Anticipation**	12.2%	9.6%
	Fixation	24.1%	19.6%
	Amplitude	3.5%	2.2%
N-	**Anticipation**	9.5%	8.6%
	Fixation	13.5%	15.7%
	Amplitude	7.3%	6.2%

3.3.2. Results

Analyses were done separately for the jump and the no-jump trials. For the no-jump trials I looked only at the first saccade after stimulus onset, while for the jump condition I identified all saccades, from the first after stimulus onset, up to the most accurate saccade that ended closest to the stimulus. These variables were adapted from Gaveau et al. (2008). Statistical analyses were done using repeated measures analysis of variance (ANOVA) and post-hoc pairwise comparisons were done with Bonferroni adjustment ($p < .05$). For group analyses the participants were separated into 3 groups: healthy controls (twelve subjects), patients with neglect (N+; five subjects) and patients who never showed neglect (N-; six subjects). Crawford and Howell's (1998) modified t-test was used to compare individual data with the group of healthy controls. The dependent variables are described under 3.3.2.1. and 3.3.2.2 respectively.

3.3.2.1. No-Jump

For the no-jump trials, saccade accuracy (absolute angular error) and saccadic reaction time were calculated for the first saccade after stimulus onset.

The *absolute angular error* was calculated as the distance between the landing point of the first saccade after stimulus onset and the actual stimulus location, using the X- and Y-coordinates. The ANOVA revealed a main effect for the between-subjects factor *group* (controls, N+, N-) [$F_{(2,20)}$=7.2, p<.01] (table 3.11 and fig. 3.11). Pairwise comparisons showed that the controls performed significantly better with more accurate saccades (absolute angular error 2.19 degrees) than the N+ group (absolute angular error 4.19 degrees; p<.01) and the N- group (absolute angular error 3.71 degrees; p<.05). There was no difference between the N+ and N- group (fig 3.11).

Table 3.11: ANOVA with the factor *group* for the absolute angular error.

		df	F	Sig.
Between-Subjects Effect	**Group**	2	7.19	.004
	Error	20		

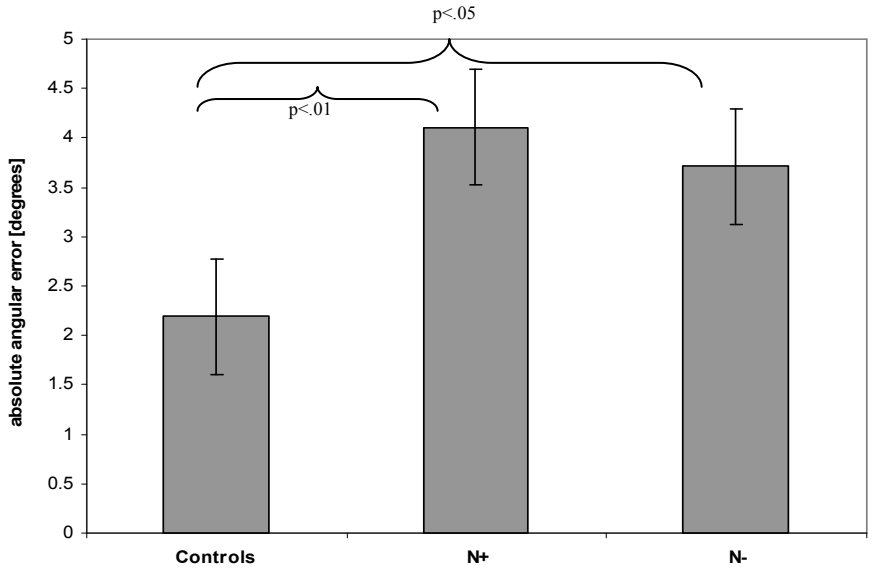


Fig. 3.11: Absolute angular error in degrees, means for controls, the N+ and the N- group. Error bars show +/- 1 standard error.

On an individual level, a modified t-test (Crawford & Howell, 1998) revealed, that three N+ patients were significantly impaired compared to the healthy controls (PI and JH: $p<.01$; MM: $p<.05$; two-tailed). For N- patients, two participants showed a decreased accuracy (WG: $p<.001$; DG: $p<.05$; two-tailed) (for the individual data please also see table 3.13).

Another univariate ANOVA with the between-subjects factor *group* was done for the *saccadic reaction time* of the first saccade but no difference was found between the groups (table 3.12) or for any individual patient. For a summary of the data please see table 3.13.

Table 3.12: ANOVA with the factor *group* for the SRT.

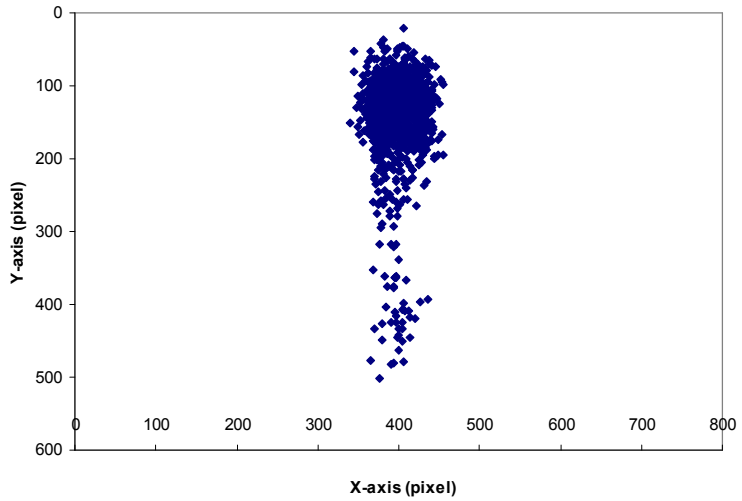
		df	F	Sig.
Between-Subjects Effect	**Group**	2	.964	.398
	Error	20		

Table 3.13: Absolute angular error (degrees) and SRT (ms) of healthy controls, N+ and N- patients for no-jump trials; means and individual data.
Significance level for Crawford & Howell's modified t-test (two-tailed): ***=$p<.001$, **=$p<.01$, *=$p<.05$.

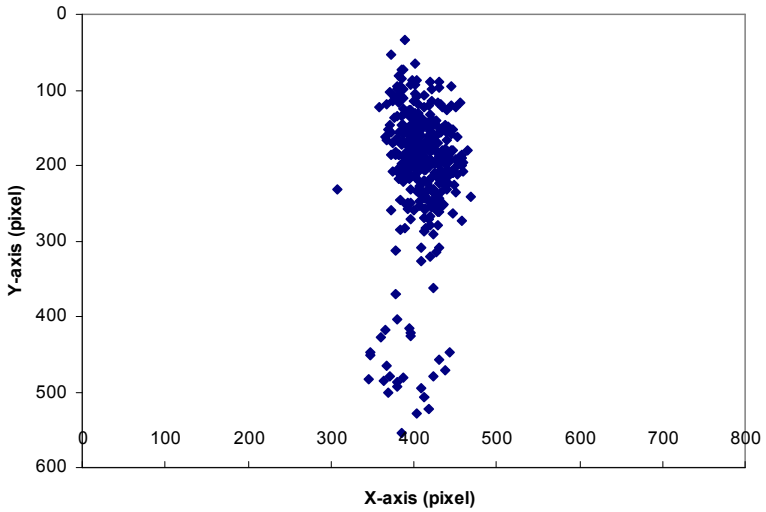
		Absolute Angular Error [degrees]	**Saccadic Reaction Time** [ms]
Controls		2.19 (SD .8)	263 (SD 37.7)
N+		4.11 (SD 1.4)	290 (SD 63.2)
N-		3.71 (SD .1.3)	291 (SD 52.1)
N+	**PI**	4.91**	359
	MM	4.55*	237
	JK	1.96	236
	JH	5.42**	261
	AK	3.69	359
N-	**RM**	3.65	205
	DG	4.57*	327
	WG	5.84***	255
	JS	2.64	300
	AM	2.36	345
	JC	3.18	317

Although the control group performed significantly better with a smaller absolute angular error compared to the N+ and N- group, the accuracy of all three subject groups seemed to be reduced with most saccades falling too short. Furthermore, a look at the individual landing points of the first saccade in the no-jump trials revealed a slight tendency to saccade to the right side for the N+ and N- group (fig. 3.12 a-c).

a)



b)



c)

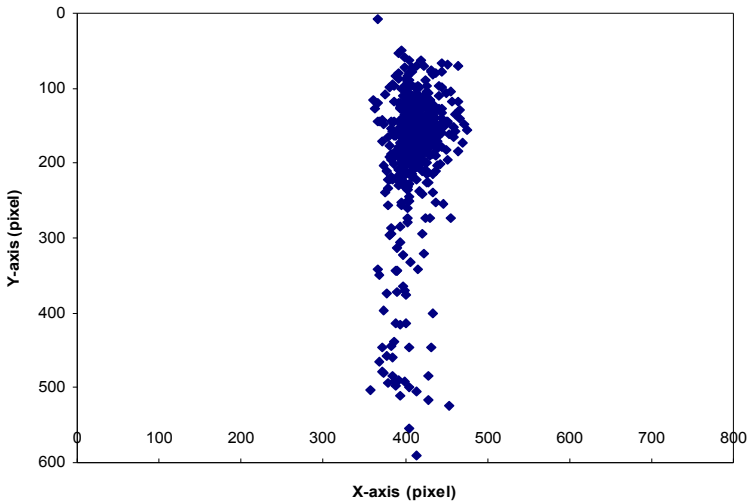


Fig. 3.12: Individual landing points of first saccade in no-jump trials of the healthy controls (a), the N+ group (b) and the N- group (c); target located at position 400,100.

3.3.2.2. Jump

For the jump trials I calculated the absolute angular error of the most accurate saccade (the one that ended closest to the target) and identified the number of saccades from the first one after stimulus onset, to the one with the smallest absolute angular error, i.e. the most accurate saccade. Furthermore, I calculated the cumulative saccadic reaction time that was used from the first saccade to the most accurate one.

A 3x2 mixed ANOVA with *group* (controls, N+, N-) as a between-subject factor and *side* as the within-subjects factor (target jump left, target jump right) revealed no significant differences regarding the *absolute angular error* (tables 3.14 and 3.17). All three participant groups were able to saccade with similar accuracy towards the targets.

Table 3.14: ANOVA with the factors side and group for absolute angular error

		df	F	Sig.
Within-Subjects Effect	**Side**	1	.018	.896
	Side x Group	2	.437	.652
	Error (Side)	20		
Between-Subjects Effect	***Group***	*2*	*162*	*<.001*
	Error	20		

Next I looked at the *number of saccades* the participants needed to reach the smallest absolute angular error. Again a 3x2 mixed ANOVA with *group* (controls, N+, N-) as a between-subjects factor and *side* (target jump left, target jump right) as within-subjects factor was done. I found a main effects for *side* [$F_{(1,20)}$=8.3, p<.01] with all participants making significantly more saccades towards left targets (2.4 saccades) compared to right targets (2.3 saccades) (tables 3.15 and 3.17; fig. 3.13).

Table 3.15: ANOVA with the factors side and group for number of saccades. Significant main effects and/or interaction in italic.

		df	F	Sig.
Within-Subjects Effect	**Side**	*1*	*8.259*	*.009*
	Side x Group	2	1.203	.321
	Error (Side)	20		
Between-Subjects Effect	***Group***	2	.280	.759
	Error	20		

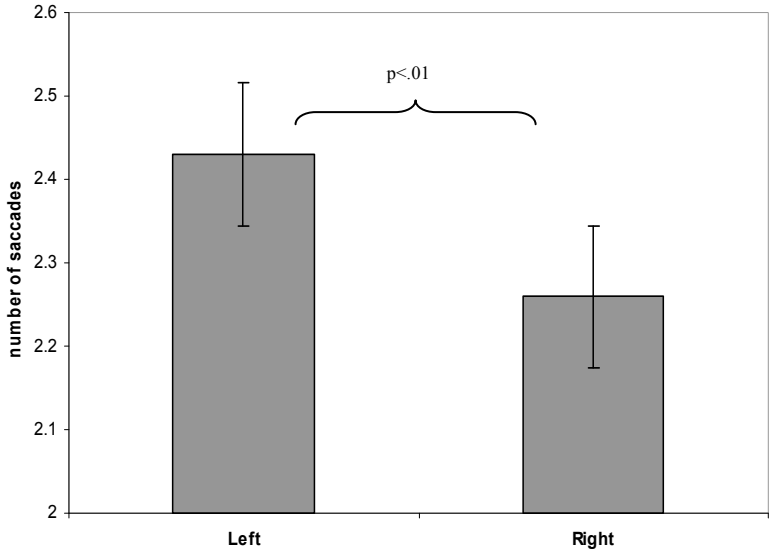


Fig. 3.13: Number of saccades used for smallest absolute angular error. Overall means for left and right target jumps. Error bars show +/- 1 standard error.

Finally a 3x2 mixed ANOVA was done for the *cumulative saccadic reaction time* with *group* (controls, N+, N-) as a between-subject factor and *side* (target jump left, target jump right) was done. I found a main effects for *side* [$F_{(1,20)}$=10.5, p<.01] with all participants having significantly longer latencies towards left targets (569 ms) compared to right targets (517 ms) (tables 3.16 and 3.17; fig. 3.14).

Table 3.16: ANOVA with the factors side and group for number of saccades. Significant main effects and/or interaction in italic.

		df	F	Sig.
Between-Subjects Effect	***Side***	*1*	*10.509*	*.004*
	Side x Group	2	1.477	.252
	Error (Side)	20		
Within-Subjects Effect	**Group**	2	.849	.443
	Error	20		

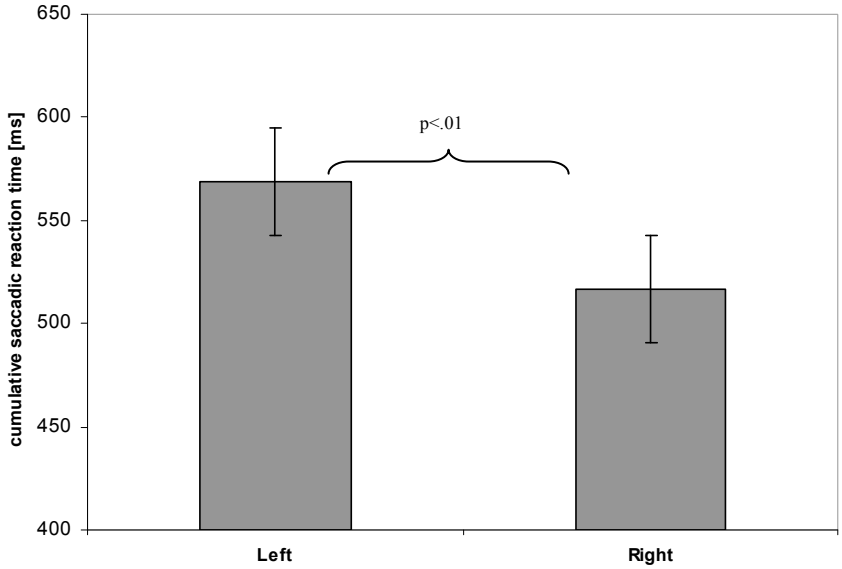


Fig. 3.14: Cumulative saccadic reaction time until the smallest absolute angular error was reached. Overall means for left and right target jumps. Error bars show +/- 1 standard error.

For a summary of all individual and group data please see table 3.17.

Table 3.17: Absolute Angular Error (degrees), number of saccades and SRT (cumulative (ms)) of healthy controls, N+ and N- patients for jump trials (separately for left and right jumps); means and individual data.
Significance level for Crawford & Howell's modified t-test (two-tailed): ***=*p*<.001, **=*p*<.01, *=*p*<.05.

		Absolute Angular Error [degrees]		**Number of Saccades**		**saccadic reaction time** [ms] **(cumulative)**	
		Jump Left	**Jump Right**	**Jump Left**	**Jump Right**	**Jump Left**	**Jump Right**
Controls		.9 (SD .4)	.86 (SD .3)	2.3 (SD .3)	2.3 (SD .4)	527 (SD 75)	508 (SD 96.9)
N+		1.28 (SD .4)	1.19 (SD .8)	2.5 (SD .5)	2.3 (SD .4)	592 (SD 95.6)	535 (SD 80.6)
N-		1.31 (SD .4)	1.23 (SD .3)	2.5 (SD .2)	2.2 (SD .4)	588 (SD 58.9)	510 (SD 52.4)
N+	**PI**	1.81*	2.61***	2.3	2.2	585	643
	MM	0.94	1	3.3**	2.9	544	456
	JK	1.22	1.13	2.1	2	465	475
	JH	1.3	1.08	2.1	2	653	504
	AK	.7	.58	2.8	2.5	712*	595
N-	**RM**	1.04	1.42	2.3	2	495	444
	DG	.77	.98	2.6	2.5	598	559
	WG	1.87*	1.09	2.4	2.5	567	565
	JS	1.04	.83	2.6	2.5	626	519
	AM	1.5	1.71*	2.5	1.4	669	449
	JC	1.64	1.38	2.5	2.3	572	523

3.3.3. Discussion

In the previous experiment (chapter 3.2) I demonstrated that all participants performed worst for the memory-guided condition compared to the immediate condition but nevertheless patients with hemispatial neglect showed the greatest performance decrease, with the largest difference scores. While most of the patients were able to perform on-line tasks like immediate saccades towards visible targets (see chapter 3.2), with this current experiment I now took a more in depth look at the patients' ability to carry out stimulus-driven, on-line saccades. This task was designed to examine a specific form of on-line tasks, namely on-line corrections.

Stationary trials (no-jump)

To my surprise, I found a group effect for the unperturbed, stationary trials. As in the previous experiments (chapter 2) and as also done by Gaveau et al. (2008) I looked at the first saccade in this simple stimulus-driven unperturbed condition. While none of the participants differed in their saccadic reaction times, the neglect and no neglect stroke patients performed worse in these trials with a greater absolute angular error compared to the healthy control participants. Yet I found in the previous chapter 2 that the patients were able to accurately carrying out pro-saccades towards targets, for the N+ group towards right targets in particular, and that they could also saccade towards the target with one eye movement.

A possible reason for the increased absolute angular errors here could be the distance between the fixation (start) point and the target. In the two previous studies (chapter 2) the target was presented on a horizontal line at 7.2 degrees away from the fixation point while in this experimental setting, the target was 15.4 degrees away at the top of the screen on a vertical line. As the stroke patients were able to accurately

saccade towards the perturbed targets by using more than one saccade, I also looked at the follow-up saccades in the unperturbed trials, and it became clear that the patients needed more saccades to get closer to the target (comparable to the jump trials). Furthermore, the stroke patients showed a slight tendency towards the right side, which also might have increased the absolute angular error compared to the healthy controls who saccaded in a straight line towards the target. Ipsilesional biases in neglect patients have been found repeatedly in other studies (e.g. Girotti et al., 1983; Duhamel et al., 1992; Niemeier & Karnath, 2003) and likewise I have reported that neglect patients show greater difficulties to inhibit pro-saccades towards right stimuli compared to left stimuli (chapter 2).

Looking at the first saccade of the healthy controls, I found that their accuracy was better compared to the stroke patients when they saccaded towards the stationary targets. However, the absolute angular error of the controls was still greater than for the perturbed trials in which more than just the first saccade were considered for identifying the most accurate eye movement. Healthy controls were able to perfectly saccade towards the left and right targets in the previous tasks (chapter 2). Thus I suppose that the distance and/or saccade direction (vertical) might have influenced the performance of all participant groups, although the stroke patients were more affected than the controls. Furthermore, I found no difference between the N+ and the N- group, thus showing that this impairment is not neglect specific.

Jump trials

For the perturbed targets on the other hand, the results showed that stroke patients with and without neglect were able to adjust their saccades just as well as the healthy controls. I did not find any differences between the N+, the N- and the control group regarding accuracy (absolute angular error), number of saccades to get closest to the

target and saccadic reaction time. Thus the data are in line with my prediction that the patients are not impaired for on-line oculomotor corrections.

The on-line correction data is thus in line with Milner and Goodale's visual pathway theory (1995, 2006, 2008). As outlined before they argue that the dorsal stream is supposed to be involved in the guiding of actions and works in real time, thus being implicated in on-line corrections towards a presented target. Neglect patients tend to suffer from lesions sparing the dorsal stream (Mort et al., 2003; Karnath, Ferber & Himmelbach, 2001) and in line with this I failed to find any on-line oculomotor impairments in these patients as a group. Moreover I found that the three of my stroke patients whose performance significantly differed from the healthy controls for the jump trials, had parietal lesions (patients PI, MM, AK) possibly involving the visual dorsal stream. PI showed an increased absolute angular error to both sides and MM needed more saccades to reach her most accurate saccade compared to the healthy controls. Furthermore, AK showed increased latencies to left targets. It has to be granted though that the deficits in these patients were selective and not general impairments that involved more than one variable or problems to both sides. Only PI showed accuracy problems to both sides yet his latencies and number of saccades appeared within the normal range (also as mentioned in the discussion of the previous experiments, PI's data is based only on a few trials and thus has to be interpreted very carefully). Finally, it has to be mentioned that another patient with a parietal lobe lesion (JH) did not show an impairment at all. These results could thus provide further evidence for the PPC (dorsal stream) being involved in on-line correction but more data is needed from patients with appropriate lesions.

With this current study I aimed to find evidence for a dissociation between saccadic on-line corrections in patients with hemispatial neglect compared to the behaviour previously described for optic ataxic patients: As stated in the introduction, it

has been repeatedly reported that optic ataxia patients, whose PPC lesions are supposed to affect the visual dorsal pathway while their ventral stream remains intact, perform better in tasks in which they can use memorised information about the target compared to tasks in which an on-line correction is required. Compared to healthy control subjects they show longer latencies or more movements to adjust their response to a suddenly changing target (e.g. Milner et al., 2001; Pisella et al., 2000). As predicted I found the opposite pattern in this experiment: My data showed that most neglect patients and stroke patients without neglect were able to perform visually guided saccadic on-line corrections towards target jumps. They did not show greater absolute angular errors, more saccades or longer latencies for the perturbed trials than the controls. Furthermore, on an individual level I found that patients with parietal lobe lesions (possibly involving the dorsal stream) performed worst in this task.

Design Issues

There is a big caveat to my argument however: In this study I was planning to take a closer look at on-line performances and particularly on-line corrections that were supposed to be carried out automatically. Unlike other studies that report that the subjects were unaware of the perturbed targets (e.g. Goodale, Pelisson & Prabanc, 1986; Pelisson et al., 1986), all participants in my study said that they had noticed the occasional target jump. This in itself may not be too problematic as in Pisella et al's study (2000, although on reaching this study is most comparable to my study) on automatic on-line corrections ("autopilot"), their participants had to point towards targets and additionally respond verbally when they detected a target jump. Thus they were also aware of the location change. So is a response still automatic when the change is detected? Pisella et al. (2000) concluded from their data that the autopilot occurred

between 200 and 300 ms after response onset and that the fast responses within this time window would be hard to stop once they were started.

Looking at my task, for the perturbed targets the saccadic reaction times were much longer than 200 - 300 ms until the most accurate saccade was reached. Thus the actual oculomotor correction was not automatic according to Pisella et al.'s criteria. However, in Pisella's study the on-line corrections were done with pointing movements, so the experiments are not directly comparable, yet I have to accept the possibility that my task was not as automatic as I hoped.

Moreover, another reason for the long saccadic reaction times in the perturbed trials might have been that perturbed and unperturbed trials were interleaved and this complexity might have caused the participants, in particular the patients, to perform more cautiously. Although all participants could see the target jump, they could not predict if the following trial was a jump or a no-jump trial. One might expect that the participants became more cautious once they had experienced the interleaved jump and no-jump trials, which could have resulted in increased reaction times and absolute angular error towards the end of the experiment. However, when I took a closer look at the individual trials I did not find a general difference between the first 25 no-jump trials a participant performed and the last 25 no-jump trials.

The study that can shed the most light on my findings is the Gaveau et al., (2008) work from which we adapted our variables (this study investigated on-line oculomotor as well as on-line reaching corrections). If I compare the variable they describe as Time to visual capture with my cumulative reaction time, the numbers in the healthy control groups are in fact very similar and my neglect group is much faster than the 2 optic ataxic patients they describe. Gaveau et al. (2008) take their data as evidence that patients suffering from optic ataxia show an impairment in the fast updating of target location. Thus according to their criteria my data could be interpreted as a sparing

of fast updating in patients with neglect. As in my study they had jump trials interleaved with stationary trials but in their design subjects were not aware of the target jump. This something I would have to address in a follow up experiment to strengthen my argument. Also looking at the number of saccades reported in the Gaveau et al. (2008) study, I have to concede that my participants made more than 2 saccades on average, whereas in the Gaveau study only the 2 optic ataxia patients showed this behaviour. Again this weakens my argument that my task involved automaticity and in a follow up experiment I will have to change my task to reduce these numbers.

So although the experimental design turned out to be problematic and possibly not suitable to test automatic on-line corrections, I can still report that stroke patients with and without neglect were able to perform on-line corrections towards perturbed targets although they might not have been automatic (but see Gaveau et al. (2008). Furthermore, the few impairments that were found were linked to patients with parietal lesions although I cannot say in more detail if there lesions were similar to those described for optic ataxia.

3.4. General Conclusions

Milner and Goodale (1995, 2006, 2008) proposed in their model that the visual dorsal stream, which proceeds form the striate cortex to the PPC, is involved in immediate action (on-line) and the visual ventral stream, which proceeds from the striate cortex to the inferior temporal cortex, plays a crucial role in off-line (e.g. memory-guided) actions. While this theory has often been supported by findings on visual form agnosia patient DF, who has a lesion to her ventral stream, and optic ataxia patients, who frequently show damage to the dorsal stream, more recently these results were extended by studies examining neglect patients. Indeed, neglect patients showed similar behaviour to patient DF, i.e. they were impaired in off-line actions and showed no deficits in on-line tasks (e.g. Rossit et al., 2009b).

In this chapter I examined the **oculomotor** behaviour of neglect patients further with regard to the dorsal-ventral stream dichotomy. In the first experiment I tested the delayed, memory-guided performance (off-line action) and immediate, stimulus-driven performance (on-line action) towards lines. As expected with regard to Milner and Goodale's model and to a previous study on neglect patients that used immediate and memory-guided pointing tasks (Rossit et al., 2009b), the N+ group in this experiment performed worse in the delayed line condition compared to the immediate line condition. For the delayed, off-line condition, they were significantly impaired compared to the healthy controls. However, no difference between the N+ and N- group was found, thus the impairment for off-line action may not be neglect specific, unlike the data described in Rossit et al. (2009b). Yet in line with Rossit et al. (2009a), I reported that the patients, who performed worst in the delayed condition, often had a temporal lobe lesion and I further assumed that these lesions could possibly be areas that are connected to ventral stream structures.

In the second experiment of this chapter I then took a closer look at the oculomotor on-line performance of the neglect patients, which, in accordance with previous findings (Himmelbach & Karnath; 2003) and as predicted from Milner and Goodale's model showed no deficits. However, the design of the task, that was adopted from previous pointing studies (Pisella et al., 2000; Blangero et al., 2008; Rossit & Harvey, 2008, and one study that combined reaching and eye-movements (Gaveau et al., 2008), revealed saccadic reaction times possibly too long to be deemed automatic (but see Gaveau et al., 2008) and unfortunately participants were also aware of the target shift so no firm conclusions can be drawn from this study. So although I found that most neglect patients were able to perform on-line, stimulus-driven saccades towards perturbed targets these might not have been automatic. On the positive side, I also found that parietal lobe lesions were often connected with a failure to perform this on-line task and I concluded that these lesions could be part of the dorsal stream that is involved in the processing of immediate on-line corrections.

In summary, my data support that, as expected, neglect patients are impaired in off-line actions but able to perform on-line tasks. However, assured statements about particular brain areas cannot be made, as my neglect patients varied a lot regarding the damaged brain regions. More patients with theory conform inferior parietal or temporal vs. more superior parietal (PPC, dorsal stream) lesions have to be tested. Furthermore, improved designs for the delay and the automatic on-line tasks have to be tested to assess these particular kinds of oculomotor off and on-line actions further.

Chapter 4

OCULOMOTOR BEHAVIOUR IN VISUAL FORM AGNOSIA PATIENT DF: ON-LINE AND OFF-LINE PERFROMANCE

4.1. Introduction

As described in the previous chapters, over the last 15 years, Milner and Goodale (1995; 2006; 2008) have proposed and refined their influential theory that distinguishes between the visual ventral stream and the visual dorsal stream. The visual dorsal stream, projecting from striate cortex to the PPC, works in real-time for immediate use in guiding actions, the ventral stream, projecting from striate cortex to infero-temporal cortex, is supposed to drive visual perception. It represents a target object long-term to allow object characteristics to be maintained over time and therefore aids object recognition across different viewing conditions.

Strong evidence for this model comes from patient (DF) who suffered from carbon monoxide poisoning in 1988 and as result developed visual form agnosia (Milner et al., 1991). A recent MRI study by James et al. (2003) has shown bilateral lesions in the LO areas in the ventral streams and furthermore a small lesion in the left PPC. DF's primary visual cortex is spared (fig. 4.1).

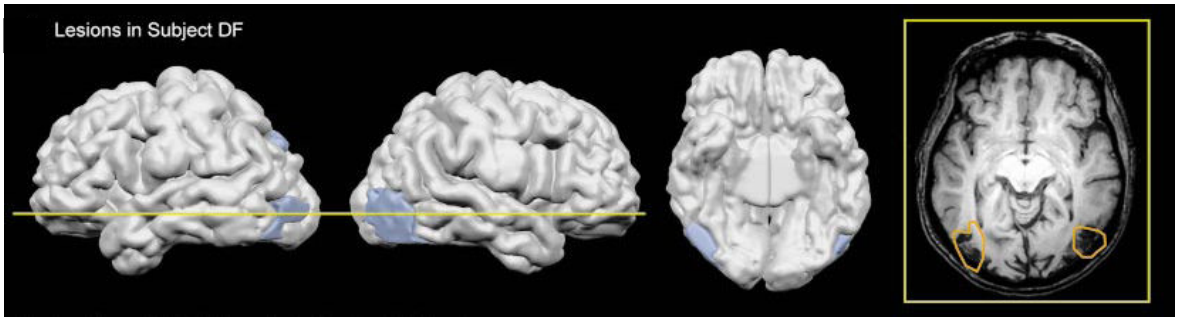


Fig 4.1.: Lesions of patient DF. It shows lesions in the ventrolateral occipital regions, sparing V1 and a small left PPC lesion. Pictures show the lateral view of the right and left hemisphere and a ventral view of the brain underside (Figure from James et al., 2003 with permission from Oxford University Press, Licence No 2925541171039)

James et al. (2003) also found abnormal brain activation that was connected to DF's impairment in perceptual tasks. While the LO cortex of healthy participants showed different responses for line drawings of common objects compared to scrambled lines, no such activation difference was observed for DF. Indeed there are observations that she shows problems to identify line drawings. However, some ventral-stream activation was found when she looked at coloured and grey-scale pictures, which she can identify more often compared to line drawings. On the other hand James and colleagues found the expected dorsal stream activations during object grasping.

In the following I will give an overview of studies that were done to examine DF's differential perception and action performance during different kinds of tasks (4.1.1) framing them in the theoretical context (4.1.2) and ending with a rationale for the experiments I carried out with DF.

4.1.1 Action and perception performance of patient DF

Previous tests with DF (Milner et al., 1991; Humphrey et al., 1994) have demonstrated severely impaired object perception. Her ability to recognise letters or line drawings is very poor but she is able to print and draw from memory (Milner et al., 1991). Despite her deficits, her preserved colour, tactile and auditory recognition help her to recognise real objects (Humphrey et al., 1994). She further has relatively normal low-level visual functions in that she can detect light flashes and high spatial frequency gratings (Milner & Goodale, 1995).

One important finding is that DF shows greater problems to make judgements or estimations about objects compared to tasks in which she directly interacts with the object. Goodale and colleagues (1991) presented her with two rectangular blocks at the same time and she couldn't distinguish between them, e.g. was not able to tell if they

were the same or different. Also, she performed very poorly when she was asked to indicate the width of a single block with her index finger and thumb without directly interacting with the object. Goodale and Humphrey (1998) also reported that DF was severely impaired in judging if two objects of random shapes were the same or different. However, when she was allowed to pick up blocks, the aperture between her index finger and thumb changed systematically in relation to the object size (Goodale, et al., 1991). Moreover, DF was able to adjust her grip aperture and hand orientation to variations in size and orientation of target objects. She even adjusted her grasp well in advance of target contact (Carey, Harvey & Milner, 1996). Likewise, her grasp did not differ from healthy control subjects when she picked up objects of random shapes (Goodale & Humphrey, 1998). In fact she used the same points of contact when gripping the shapes with index finger and thumb.

To take a closer look at DF's grasping ability Dijkerman, Milner and Carey (1998) used circular transparent discs with two and three holes cut in them as targets. DF was asked to reach out and grasp these discs by inserting her fingers through the holes. While she had previously demonstrated that she could perfectly grasp objects (e.g. blocks), she completely failed to adjust her grip and hand orientation in relation to the holes and needed tactile cues, i.e. her hand touching the disc during the attempt to grip it, to correct her hand posture. Her grasp performance was worse for the three-hole task but also still impaired when the disc had only two holes.

To examine this impairment in the hole-grasping performance closer, McIntosh et al. (2004) asked DF to grasp rectangular blocks, which varied in the amount of transparent and non-transparent areas, through two square holes. Again DF failed to grasp any of the presented target blocks correctly.

Another task tested DF's ability to place her hand (or a hand-held card) in slots of different orientations (Goodale et al., 1991). She showed great difficulties to verbally

indicate the orientation. She was also impaired to manually indicate the orientation (i.e. rotating her hand or the card) without actually acting towards the slots. On the other hand, DF showed a good ability to reach out and to place her hand or card into the slot. However, limitations to DF's ability to interact with objects become obvious when she is confronted with more complex targets. For example she shows problems to deal with cross-shaped objects where the grip orientation is not controlled by one single principal axis (Carey, Harvey & Milner, 1995). Likewise, she was impaired to post T-shaped objects through a slot while she was able to do that with a simple card (Goodale et al., 1994b).

When DF was asked to point at designated coloured tokens, she showed no problems. She was able to point at a particular one out of a set of different tokens, at a nominated sequence of up to five tokens as well as two tokens simultaneously with the forefingers of both hands (e.g. Murphy, Racicot & Goodale, 1996; Carey, Dijkerman & Milner, 2009). Nonetheless she was unable to reproduce the token array in front of her on a separate board or to perform bi-manual pantomime pointing movements. Here she showed a great impairment even when the original array remained visible all the time (e.g. Murphy, Racicot & Goodale, 1996; Carey, Dijkerman & Milner, 2009). Murphy, Racicot and Goodale (1996) for example reported that her response was inaccurate and slow, yet it showed resemblance to the original array, for example she placed the red token to the right of the blue token or the yellow one below the green one. Furthermore, she was unable to indicate the spatial location of a single individual target by pointing to its equivalent position on the response board (Carey et al., 2006). However, DF could enumerate the number of presented tokens and judge which two tokens were, for example furthest apart or closest to one another, although her answer was slow and she used larger and more frequent head movements to complete this task, compared to the control participants.

In another study, Carey, Dijkerman and Milner (1998) examined DF's processing of depth. DF was asked to reach for target cubes of three different sizes that were located at five possible distances. The results showed that she was able to process the 3D distance very well and her movements were as accurate as the grasping of the control group. Furthermore, the peak velocity of her grasping correlated highly with the actual object distance in the monocular and binocular condition. However, when she was asked to make a verbal estimation of the distance, it correlated with the distance under binocular view only and even here it was worse than for the healthy controls.

In a second experiment by Carey, Dijkerman and Milner, DF had to point towards a single lit LED that was presented at one of 16 different random positions in front of her on the table. The results showed that her pointing movements were less accurate under monocular viewing, but the amplitude of DF's pointing movement still correlated highly with the target distance. The authors therefore suggested, that although binocular vision is important for DF to point accurately, monocular vision is enough to reach sufficient endpoint accuracy.

Dijkerman, Milner and Carey (1997) also tested DF's immediate and delayed responses. She showed no impairment when she had to execute simple eye-movements or pointing movements towards a single visible target that was presented at one of eight possible locations on a horizontal axis. Her immediate responses were as accurate as the pointing movements and saccades of the healthy controls subjects, but as soon as she was asked to perform delayed pointing and saccades towards targets, i.e. she had to wait five seconds after the target disappeared before making a response, her eye and hand movements became considerably inaccurate.

4.1.2. DF's performance in relation to the dorsal- and ventral visual stream

A closer look at DF's performance shows that it is in line with her dorsal stream being mostly intact and her ventral stream lesioned (James et al., 2003). She shows very good responses when she interacts with presented objects and even acts systematically in accordance with varying target characteristics. DF is not only able to point or saccade towards single targets (Murphy, Racicot & Goodale, 1996; Dijkerman, Milner & Carey, 1997) or sequences of designated coloured tokens (Carey et al., 2006), she also shows an accurate guidance of hand and finger movements when placing her hand into a slot (Milner et al., 1991) or when she is required to pick up an object when binocular view is possible (Goodale et al., 1991; Carey, Harvey & Milner, 1995; Carey, Dijkerman & Milner, 1998). However, although she can accurately interact with targets she is unable to explicitly report the object characteristics. McIntosh and his colleagues (2004) therefore suggested that dorsal stream processes do not involve visual awareness.

Indeed, DF is unable to comment on the size, shape or orientation of visual objects (Goodale et al., 1991; Milner et al., 1991). Furthermore, she is severely impaired for memory guided actions like delayed saccades and delayed pointing for example (Goodale, Jakobson & Keillor, 1994; Dijkerman, Milner & Carey, 1997; Rossit et al., 2010) which is in line with previous findings that the ventral stream is involved in maintaining object characteristics over time for delayed responses (off-line), while the dorsal stream works in real time for the immediate (on-line) use of information (Westwood and Goodale, 2003).

Also the complexity of an object interferes with DF's performance. While she is able to process simple objects, she is unable to correctly interact with objects of more complex shapes. For example she is impaired when grasping objects via holes cut into them (e.g. Dijkerman, Milner & Carey, 1998) or T-shaped objects (Goodale et al.,

1994b). McIntosh et al. (2004) suggested that an intact ventral stream is necessary to respond to complex stimuli while simple objects are directly processed by the dorsal stream. Likewise Carey, Harvey and Milner (1995) observed DF's impairment for grasping complex everyday tools by the correct part of the object (e.g. the handle of a knife) and concluded that the visual processing capacities of the dorsal stream are limited but that residual visuomotor abilities are still present in patient DF. Furthermore, Carey, Harvey and Milner assumed that semantic errors are involved in DF's impaired interaction with everyday tools as the tool has to be recognised first before an appropriate grasp can be executed.

Another approach to explain DF's failure comes from differences in processing egocentric and allocentric information (Dijkerman, Milner & Carey, 1998; Carey et al., 2006;). Dijkerman, Milner and Carey (1998) concluded that for the accurate gripping of a transparent disc by holes that were cut into it, both allocentric and egocentric information have to be processed. Furthermore, they presumed that these processes require ventral and dorsal stream involvement. While the dorsal stream guides the forefinger into the holes and leads the hand position by rotating the wrist to its correct orientation, the ventral stream provides allocentric information for the forefinger and thumb grasp to choose the correct holes. Indeed, when DF was asked to grasp a disc, she was only able to use the egocentric information that guided her hand to the appropriate part (left or right) of the disc. At the same time she was completely unable to use allocentric information to adjust her grip to the inter-hole distance. This failure occurred not only for discs with three holes but also for the simple condition in which she had to grasp a disc by only two holes and.

Further evidence for the egocentric and allocentric dissociation in relation to the ventral and dorsal stream model came from an experiment by Carey et al. (2006). The authors attributed DF's good performance to point directly towards a sequence of token

to her ability to use egocentric visual coding for this task by monitoring her own movements. Likewise she was able to point towards two tokens simultaneously with both hands (Carey, Dijkerman & Milner, 2009). Carey and his colleagues presumed that she coded the location of each target separately, to guide two independent responses without being able to inter-relate the whole set of tokens. She showed the expected impairment to make allocentrical judgments of the spatial target positions and was unable to reproduce the set of tokens to an identical board next to the original one (Carey et al., 2006).

In summary, DF performs well when she interacts with visual objects directly, i.e. she is able to saccade or point towards them or to grasp them. However, when the targets are perturbed, e.g. when they are delayed, a monocular view is possible only or the objects are very complex and/or she has to verbally comment on them, her performance is clearly impaired. Furthermore, the ventral stream is presumably also involved in the processing of allocentric information and indeed DF showed severe impairments when a task required allocentric judgement while she performed perfectly when she could rely on egocentric information alone (e.g. Dijkerman, Milner & Carey, 1998; Carey et al., 2006; Carey, Dijkerman & Milner, 2009).

4.1.3. Purpose of the current experiments

In the previous chapters I reported the performance of patients with hemispatial neglect on various oculomotor tasks. The tasks I used were designed specifically to examine whether oculomotor actions may be separated in the same on-line off-line distinctions as described previously for reaching and grasping. Overall my results showed that neglect patients performed better for on-line oculomotor actions (pro-saccades, immediate saccades and on-line corrections) compared to off-line actions (anti-saccades and delayed saccades). These findings are in agreement with Milner and Goodale's

theory that the dorsal stream processes on-line and the ventral stream off-line actions and that the IPL and related structures (as implicated by Rossit et al., 2009a, 2011) may be functionally similar to the ventral stream in terms of mediating off-line processes.

However, lesion locations in neglect patients vary and therefore a concrete assignment towards dorsal or ventral stream structures or even IPL and temporal areas remains difficult. Thus, in addition to the neglect patients, I tested visual form agnosia patient DF who has repeatedly given evidence for Milner and Goodale's model of the two visual pathways. She has shown good performance for on-line (dorsal-stream) actions and deficits when she had to perform off-line (ventral-stream) tasks (Goodale, et al., 1994a; Dijkerman, Milner & Carey, 1997; see also chapter 1). These findings are in line with her LO lesions that are supposed to affect her ventral streams yet her visual dorsal stream structures are largely intact (James et al., 2003). However, most of the research that has been done on patient DF has focused on grasping or pointing tasks and only very few limited studies have examined her eye-movement behaviour. Therefore, I will test her oculomotor behaviour and I expect similar results to the reaching and grasping literature. Indeed Levy et al. (2007) have argued that saccade and arm-related activity are mostly overlapping.

To compare DF to neglect patients, she was tested with the same experiments as reported in chapters 2 (pro-saccades, anti-saccades & fixation) and 3 (memory-guided off-line action and on-line corrections) with only one exception: she was not examined with the interleaved pro-saccade and fixation task (chapter 2.3). As according to Milner and Goodale (2006), DF as well as the neglect patients are supposed to have damage to the ventral stream or ventral stream connected areas, I suppose to find similar results for the three experiments, i.e. that she is impaired for off-line actions while I expect her to show no deficits when on-line responses are required. For a detailed description of the experiments, please see chapters 2 and 3.

4.2. Experiment 1: Anti-Saccades, Pro-Saccades and Fixation

Pro-saccade tasks that require a simple stimulus-driven saccade towards an existing target are supposed to be an on-line action and, according to Milner and Goodale's theory (1995; 2006; 2008), are processed by the dorsal stream. Alternatively, for an anti-saccade, the participant has to covertly locate the target without directly looking at it and to remap its coordinates to the opposite side before saccading towards this new location. As no target is present at the mirrored location, anti-saccades require off-line actions and according to Milner & Goodale (1995; 2006; 2008) should be processed by the ventral stream and functionally related structures.

Since DF has previously shown an impairment for off-line actions (e.g. Dijkerman, Milner & Carey, 1997; Rossit et al., 2010) and as, in line with these behavioural observations, her lesions to the LO area are supposed to effect her ventral stream whilst her dorsal stream mostly remains intact (James et al., 2003), I expect her to perform well on pro-saccades and to be impaired for anti-saccades. Dijkerman, Milner and Carey (1997) tested DF briefly on anti- and pro-saccades and indeed found an impairment for anti-saccades only. However, the reason for this failure still remains uncertain.

Therefore, I used an additional fixation task to take a closer look to assess, if her expected and previously reported (Dijkerman, Milner & Carey, 1997) anti-saccade failure is an inhibition problem or rather an inability to remap the target location to the mirrored location. If she is not only impaired for anti-saccades but also for the fixation task, this might indicate that she has problems to inhibit stimulus driven saccades towards targets. However, a perfect fixation performance would indicate that she might have a vector inversion problem to remap the target location to the opposite side (for anti-saccades). As her lesion is supposed to affect her off-line performance and as she

has previously shown impairments for various off-line tasks, I expect her not to be impaired in the inhibition task. Instead I expect a vector inversion (off-line action) problem to be the cause for the expected and previously found anti-saccade errors (Dijkerman, Milner & Carey, 1997).

4.2.1. Method

Healthy Participants

Six healthy control subjects, age-matched to patient DF (2 male, 4 female, mean age 60 years, SD 6), were tested. For this control group, four healthy subjects were newly recruited and the two youngest participants of the healthy control group (see chapter 2.2.1.1.) were also included.

Patient DF

At the time of testing patient DF was 54 years old. The study was conducted in accordance with the ethical guidelines of the South Glasgow University Hospitals NHS Trust and the Declaration of Helsinki. All participants gave their informed consent prior to the study.

Apparatus, stimuli, data processing and procedure

Apparatus, stimuli, data processing and procedure were identical to the previously described study (see chapter 2.2.).

According to the before specified rejection criteria, 20% of DF's left pro-saccade trials were excluded and 20% of her right target trials. 7.9% of left target trials for the healthy controls were rejected and 11.3% of the trials with right targets. For the anti-saccade condition, 20% and 12.5% respectively of DF's anti-saccade trials with

leftward and rightward presented stimuli were excluded, and 11.4% and 12.8% respectively of the left and right target anti-saccade trials of the control subjects were rejected. Finally, 7.5% of DF's fixation trials in which a stimulus appeared on the left side were excluded and 7.5% as well of the right stimulus trials. Furthermore, 8.3 % of the left target fixation trials and 8.8% of the right target fixation trials of the healthy controls were rejected. Detailed information for each exclusion category can be found in table 4.1.

Table 4.1: Percentage of excluded trials for the anticipation, fixation and amplitude criteria, for anti-saccades, pro-saccades and fixation trials, broken down into left and right targets and presented separately for controls and DF.

		Anti-saccades		**Pro-saccades**		**Fixation**	
		Left	**Right**	**Left**	**Right**	**Left**	**Right**
Controls	**anticipation**	4.2%	6.7%	4.2%	6.7	5.4%	6.3%
	fixation	2.5%	3.8%	2.5%	3.8%	2.9%	2.5%
	amplitude	4.8%	2.4%	1.3%	0.8%	-	-
DF	**anticipation**	5%	5%	10%	5%	7.5%	7.5%
	fixation	5%	-	10%	12.5%	-	-
	amplitude	10%	7.5%	-	2.5%	-	-

4.2.2. Results

I used the modified t-test by Crawford and Howell (1998) to test whether DF's performance differed from that of the healthy controls. This test has been developed to compare the performance of a single patient to a sample of control subjects. As DF has been tested repeatedly on on-line and off-line tasks and has shown a clear impairment for off-line performances, I had a priori expectations for her to be unimpaired for pro-saccades and fixations yet impaired for anti-saccades (see also Dijkerman, Milner & Carey, 1997), hence the one-tailed p-value for the results was used. The analysed variables are identical to the variables described previously (chapter 2.2.2).

4.2.2.1. Pro-saccades

Unsurprisingly, DF and the healthy controls, performed very well in the pro-saccade condition (table 4.2). Nevertheless, DF's saccadic accuracy was impaired compared to the control group for leftwardly presented stimuli [$t_{(5)}$=2.6, p<.05]. Her left *absolute angular error* was 1.56 degrees, while the controls' mean absolute angular error was 0.66 degrees (SD 0.3). No difference was found for right targets, DF was able to make a very accurate rightward saccade with an absolute angular error of only 0.79 degrees. The absolute angular error of the control group was 1.27 degrees (SD 0.9).

Also no differences were found for the *saccadic reaction times* to both sides. DF responded to the targets as quickly as the healthy controls. Her saccadic reaction time for targets presented on the left side was 231 ms and for right targets 167 ms, whilst the control subjects reached mean reaction times of 182 ms (SD 62.4) for left targets and 195 ms (SD 54.8) for right targets.

Table 4.2: Absolute Angular Error in degrees and SRT in ms for left and right targets for controls and DF.

	Target side	Controls	DF
Absolute Angular Error	left	0.66 (SD 0.3)	1.56
	right	1.27 (SD 0.9)	0.79
Saccadic Reaction Time	left	182 (SD 62.4)	231
	right	195 (SD 54.8)	167

4.2.2.2. Anti-saccades

No difference between DF and the healthy controls was found for the *percentage of correct anti-saccades*. DF could correctly inhibit a stimulus driven saccade in 88% of the trials for leftwardly presented stimuli and in 86% for rightwardly presented stimuli and make a saccade towards the opposite side. Mean percentages of correct anti-

saccades for healthy controls were 84% (SD 13.7) for left stimuli and 79% (SD 21.7) for right stimuli.

Regarding the accuracy of correct initiated anti-saccades, DF's performance differed significantly from the healthy controls. For leftwardly presented stimuli, which required a saccade to the right side, DF's mean *absolute angular error* was 3.47 degrees, while the mean absolute angular error of the controls was 1.75 degrees (SD 0.5). DF's mean absolute angular error for rightwardly presented stimuli, which required a saccade to the left side, was 3.4 degrees and the controls performed more accurately with a mean absolute angular error of 1.62 degrees (SD 0.4). Thus DF's anti-saccade performance was significantly impaired for both sides compared to the healthy controls [left stimuli: $t(5)=3.5$, $p<.01$; right stimuli: $t_{(5)}=4$, $p<.01$] (fig 4.2).

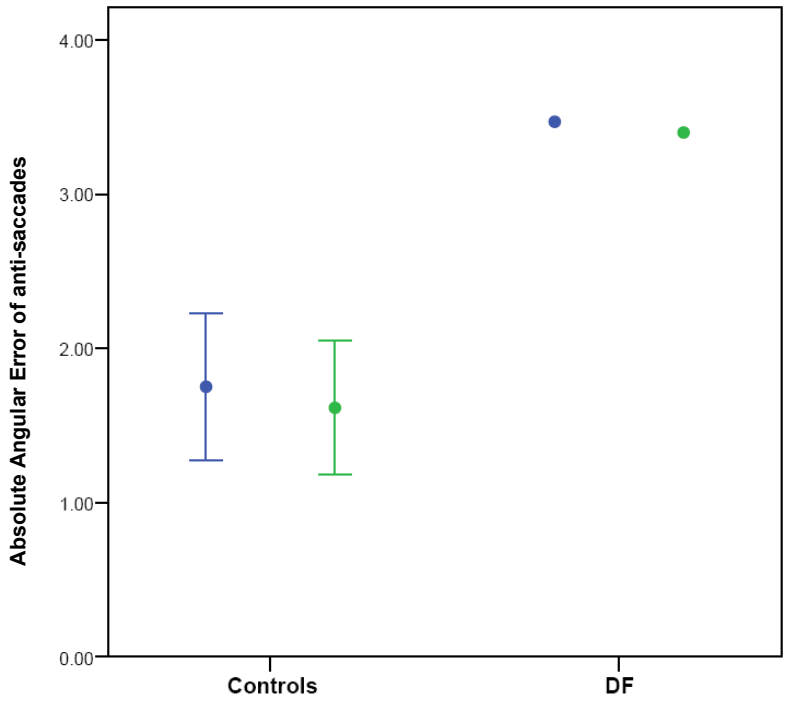


Fig. 4.2: Absolute Angular Error in degrees of left (blue) and right (green) anti-saccades for controls and patient DF. Error bars show 95% confidence interval.

Looking at the *saccadic reaction time*, DF performed more slowly compared to the healthy controls but the difference was not significant. For leftwardly presented stimuli DF's mean saccadic reaction time was 502 ms while the controls reached a mean reaction time of 328 ms (SD 114.4) for correct anti-saccades. For right targets DF's reaction time was 431 ms and 358 ms (SD 90.3) for controls respectively.

A significant difference between DF and the healthy control participants was found for the *saccadic reaction time of the erroneous pro-saccades* [left stimuli: $t_{(5)}=8.3$, $p<.001$; right stimuli: $t_{(5)}=6.1$, $p<.01$]. With 493 ms and 336 ms for left and right targets DF's latencies were much longer compared to the control's latencies (left targets: 206 ms, SD 31.6; right targets: 164 ms, SD 26) (fig. 4.3).

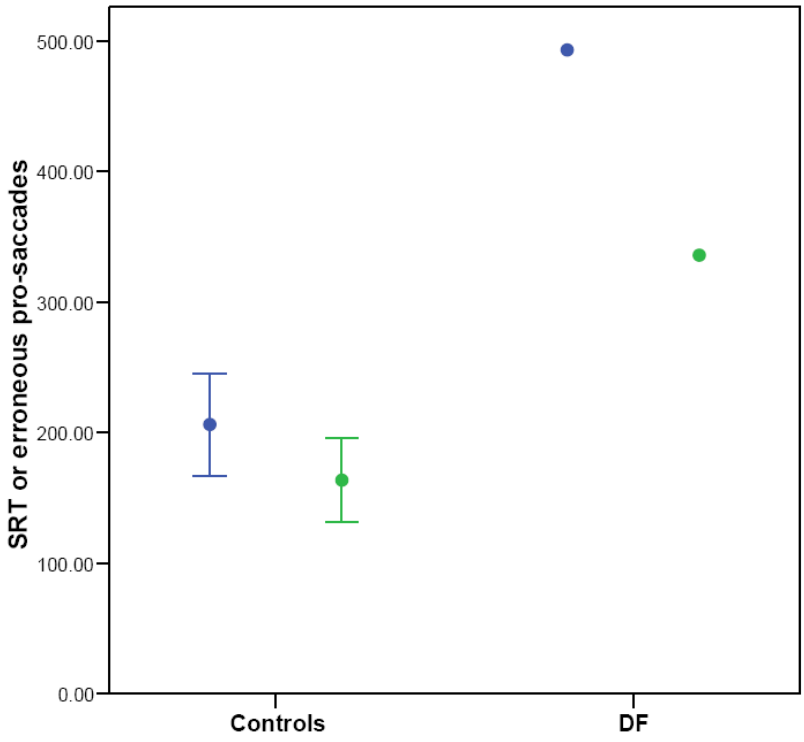


Fig. 4.3: SRT in ms of erroneous pro-saccades in the anti-saccade task for controls and patient DF. Error bars show 95% confidence interval.

Finally a look at the *corrected anti-saccades* was taken. DF did not correct any of the erroneous pro-saccades she did towards left targets and she corrected only 20% of the false saccades to right targets. The healthy controls corrected 65% and 69% respectively of erroneous pro-saccades to left and right targets. Nevertheless, the difference between DF and the controls was not significant. For a summery of DF's data please see table 4.3.

Table 4.3: Percentage of correct anti-saccades, Absolute Angular Error, SRT, SRT of erroneous pro-saccades and corrected anti-saccades for left and right targets for controls and patient DF; DF(N) = actual number of trials; (-) = not applicable

	Target side	Controls	DF	DF (N)
correct anti-saccades	left	84% (SD 13.7)	88%	28
	right	79% (SD 21.7)	86%	30
Absolute Angular Error	left	1.75° (SD 0.5)	3.47°	(-)
	right	1.62° (SD 0.4)	3.40°	(-)
SRT	left	328ms (SD 114.4)	502ms	(-)
	right	358ms (SD 90.3)	431ms	(-)
SRT of erroneous pro-saccades	left	206ms (SD 31.6)	493ms	4
	right	164ms (SD 26)	336ms	5
corrected anti-saccades	left	65% (SD 38.5)	0%	0
	right	69% (SD 39.8)	20%	1

4.2.2.3. Fixation

DF's performance in this condition was perfect. Like the controls she showed no impairment with 100% correct responses.

4.2.3. Discussion

Pro-saccades

DF's performance on pro-saccades was almost perfect. She showed no increased latencies and there was also no difference between her and the healthy controls for the

accuracy of her saccades towards right targets. As DF's dorsal stream has remained intact after her accident, her on-line actions are supposed to be unimpaired. These findings are supported by previous studies, which also found that DF is able to perform simple saccades and reach towards a target without difficulties (Milner et al., 1991; Dijkerman, Milner & Carey, 1997). However the accuracy of her saccades towards left stimuli showed a significant impairment. I know that DF has a strabismus in her right eye, thus I assume it might affect her saccades to the left side. Otherwise, I have no explanation for her unexpected problems for left pro-saccades.

Anti-saccades

On the anti-saccades task, DF showed normal latencies and the percentage of her correct saccades did not differ from those of the healthy subjects. However, the accuracy of her anti-saccades was significantly reduced. These findings are in line with DF's anti-saccade performance described in Dijkerman, Milner and Carey's study (1997). Like in the previous study by Dijkerman and colleagues, in my task she also had no difficulties to inhibit her reflexive eye movements towards the target. However, she was not able to execute an accurate saccade to the opposite location (see also Dijkerman, Milner & Carey, 1997).

Vector inversion is crucial for executing correct anti-saccades Collins et al. (2008). Thus I presume that vector inversion impairment caused DF's bilateral anti-saccade accuracy deficit. Indeed these findings support Goodale and Milner's model (e.g. 1992; 1995; 2006) of two different pathways for perception and action and it is furthermore in line with previous studies that have reported DF's impairment for off-line tasks (e.g. Goodale, et al., 1994a; Dijkerman, Milner & Carey, 1997). DF's ventral stream damage might lead to an inability to covertly gain information about the target location without looking at it, and she therefore has difficulties mirroring its position to

the opposite side to act on. On the other hand her on-line action, i.e. to make a stimulus-driven eye movement towards a target in the pro-saccade condition, is mostly preserved. Indeed, she has previously shown good performances when she directly responded towards targets (e.g. Goodale et al., 1994a; Rossit et al., 2010) but she was impaired when she had to make judgements about objects without interacting with them (e.g. Goodale et al., 1991; Milner et al., 1991).

Many studies also agree on the important involvement of the PPC in anti-saccades (e.g. Pisella, Berberovic & Mattingley, 2004; Medendorp, Goltz & Vilis, 2005; Van Der Werf et al., 2008; Nyffeler et al., 2008). DF showed a bilateral impairment for anti-saccade accuracy and besides her lesions to the LO areas of the ventral stream, damage to her left PPC has also been described (James et al., 2003). Indeed the role of the PPC in the remapping of locations has been confirmed repeatedly. For example a first PPC activation was found in the hemisphere that connects to the stimulus location but then it shifts to the hemisphere that relates to the saccade goal location (Medendorp, Goltz & Vilis, 2005; Van der Werf et al., 2008). As this activity seems to engage both hemispheres at different stages of an anti-saccade (see also Nyffeler et al., 2008), it could be assumed that DF's lesion to the left PPC impaired the process of getting information for the vector inversion for right stimuli, while for left stimuli the execution of the accurate motor saccade could have been disrupted.

However, although DF's results can support the idea that the PPC is involved in voluntary eye movements and vector inversion, her impaired anti-saccade performance is also evidence for her deficits in off-line actions that are processed by ventral stream structures which are damaged in DF. Indeed her anti-saccade problems are in line with her previous off-line task impairments (e.g. Dijkerman, Milner & Carey, 1997; Carey et al., 2006). For example Carey et al. (2006) reported that DF was able to perform pantomimed pointing movements towards a sequence of targets, but while she could

process general information like which target to point to first, the accuracy of her pointing movement towards the remembered locations was greatly impaired. Likewise the lack of erroneous pro-saccades in the anti-saccade condition showed that she had perceived the target and that she was able to saccade into the correct direction, i.e. away from the target, but at the same time her accuracy was clearly impaired.

Moreover, the analysis of the erroneous pro-saccades showed longer reaction times for DF compared to the healthy participants. In fact DF's latencies for falsely made saccades were as long as, or even longer, than her reaction times for correct anti-saccades. These results could indicate that she executed erroneous pro-saccades to get more information about the target location rather than these errors being caused by an inhibition failure. Nonetheless, DF's overall performance regarding the percentage of correct anti-saccades was excellent, her high percentage of correct anti-saccades (88% for left targets and 86% for right targets) showed that she had understood the task.

Fixation

DF had no difficulties to withhold unwanted stimulus-driven saccades towards the peripheral targets. This is no surprise as in the anti-saccade task she had shown already that she is able to inhibit eye movements under even more difficult conditions, and the results from the fixation task support these findings. DF's perfect fixation performance and the fact that she is only impaired in anti-saccade accuracy without a more than expected difficulty in inhibiting erroneous pro-saccades, supports the previous conclusion that her anti-saccade impairment is based on a vector inversion deficit that goes in line with either her PPC lesion or (as argued above) or more likely her ventral stream lesions.

Conclusion

The results of the three conditions (pro-saccades, anti-saccades and fixation) are in line with previous findings. While DF was able to execute pro-saccades (with the slight exception of the accuracy of left pro-saccades that has not been found in a repeat experiment performed since by another investigator), i.e. she showed correct on-line performance when she was required to respond to the presented target directly, her off-line accuracy performance was impaired during the anti-saccade condition. Furthermore, DF's perfect fixation condition gave evidence for her anti-saccade failure being a remapping (off-line) problem rather than a problem to inhibit saccades towards the target.

Indeed, similar results were found by Dijkerman, Milner and Carey (1997) who also tested DF on anti- and pro-saccades and Carey and his colleagues (2006) who reported of her ability to point towards targets (on-line) while she showed difficulties to perform pantomimed actions (off-line). All these results agree that DF is able to perform on-line tasks in which she has to respond to a presented target, but at the same time she is impaired in off-line tasks when the target is not available during response execution. Furthermore, these findings are in line with her lesions to the LO area which is supposed to be part of the ventral stream that is involved in off-line actions and her mostly spared dorsal stream that is involved in on-line performances. However, as DF has a left PPC as well as ventral stream lesions both areas may be involved in vector inversion processes. I cannot say for sure which lesion is responsible for her anti-saccade accuracy failure although the compromised ventral stream seems the more likely candidate in light of the other evidence described, and the likelihood that the left PPC lesion should lead to right difficulties, yet her accuracy impairments are bilateral.

4.3. Experiment 2: Memory-guided (off-line) action

In this second experiment I confronedt DF with another off-line task. This time she was required to perform delayed saccades (see also chapter 3.2). It is well known that patient DF has previously shown an impairment in delayed actions while she is able to perform normally in immediate actions (Goodale, Jakobson & Keillor, 1994; Milner & Goodale, 1995; Rossit et al., 2010). These results are in concordance with Milner and Goodale's proposal (2006; 2008) that the ventral stream, which is damaged in DF, is supposed to be involved in long-term target object representation, while the dorsal stream, which remains intact in DF, works in real-time for immediate use in guiding actions. However, what still remains to be established, and what I tried to address in the delayed saccade experiment, is whether this dissociation can be upheld for saccade processing.

A direct prediction from Milner and Goodale's model (1995; 2006) would be that stimulus triggered (immediate) saccades should be driven by dorsal stream structures (thought to be relatively spared in patient DF, see James et al., 2003) whereas memory-guided (delayed) saccades, which require the stimulus to be maintained over time, would require ventral stream involvement. Therefore patient DF should be able to execute stimulus triggered eye movements, whereas her memory-guided saccades should be compromised. Although these predictions follow directly from Milner and Goodale's model, to me this was a genuine empirical issue as many studies implicate the PPC in memory-guided saccadic behaviour (e.g. Müri et al., 1996; Nyffeler et al., 2005; and see a more detailed review in chapter 3.1.1), an area that is deemed to be relatively spared in DF. Thus this experiment was planned to shed light on the contribution of ventral stream structures to delayed action.

4.3.1. Method

Healthy participants

Six age matched control subjects to patient DF (2 male, 4 female; mean age 57.3, SD 3.6) participated in the experiment.

Patient DF

For a detailed description of patient DF, please see chapter 4.2.

Apparatus, stimuli, data processing and procedure

Apparatus, stimuli, data processing and procedure were almost identical to the study described in chapter 3.2. The only difference was that patient DF completed two blocks of 66 trials each because of a lack of time, starting with 66 trials of memory guided saccades which was followed by the 66 trials immediate saccade block. However, as the control subjects were also used for comparison with the stroke patients they performed two memory guided blocks (2 x 66 trials) and one immediate saccade block (66 trials). Therefore I only used the first memory-guided saccade block of the healthy controls for a comparison with patient DF.

The exclusion criteria of too short latencies, improper fixation and too small saccade amplitudes resulted in a rejection of 14.4% for the stimulus-driven, immediate saccade trials for the healthy controls and 15.2% for DF. For the memory-guided saccade trials, these numbers were 20.5% and 16.7% respectively, thus showing no differences between DF and the control subjects. Detailed information for each exclusion category can be found in table 4.4.

Table 4.4: Percentage of excluded trials for the immediate saccade and delayed saccade trials, presented separately for controls and DF.

		immediate saccades	delayed saccades
Controls	**Anticipation**	6.6%	6.2%
	Fixation	22.8%	2.8%
	Amplitude	5.1%	5.1%
DF	**Anticipation**	4.5%	1.5%
	Fixation	-	13.6%
	Amplitude	10.6%	1.5%

4.3.2. Results

To test whether DF's performance differed from the control sample I used the modified t-test by Crawford & Howell, 1998. As previously stated, DF has been tested repeatedly on on-line and off-line tasks and has shown a clear impairment for off-line performances. Therefore I had an a priori expectation for her to be unimpaired for immediate yet impaired for delayed saccades (see also Dijkerman, Milner & Carey (1997), hence the one-tailed p-value for the results was used. For more information about the analyses of this task please see 3.2.

4.3.2.1. Percentage of correct saccades within 30 degree

No difference was found between DF and the healthy controls for stimulus-driven saccades when she was allowed to look at the target line immediately. With 100% correct saccades for each direction her performance was just like that of the controls (who performed 99% correct). She clearly had no problems with this task (table 4.5).

In the memory-guided saccade condition control participants performed very accurately again with 97.4% (SD 4), 94.8% (SD 7.4) and 97.3% (SD 4.4) correct saccades for left, central and right lines. With 66.7% and 89.5% correct saccades for left and right lines, DF was significantly impaired in her memory-guided responses on the

left [$t_{(5)}$=-7.1, p<.001] when compared to the controls. For the rightward targets there was, however, a trend [$t_{(5)}$=-1.6, p=.081]. Closer inspection of the data showed that this lack of effect for the rightward stimulus was driven by a single control participant who performed much poorer than the other five (his performance was more than 3 SDs away from the mean of the other five subjects, with only 89% correct vs. the average of the other five controls of 99% correct)[1]. Nevertheless, she was never impaired for centrally presented lines with 94.4% correct saccades (see fig. 4.4 and table 4.5).

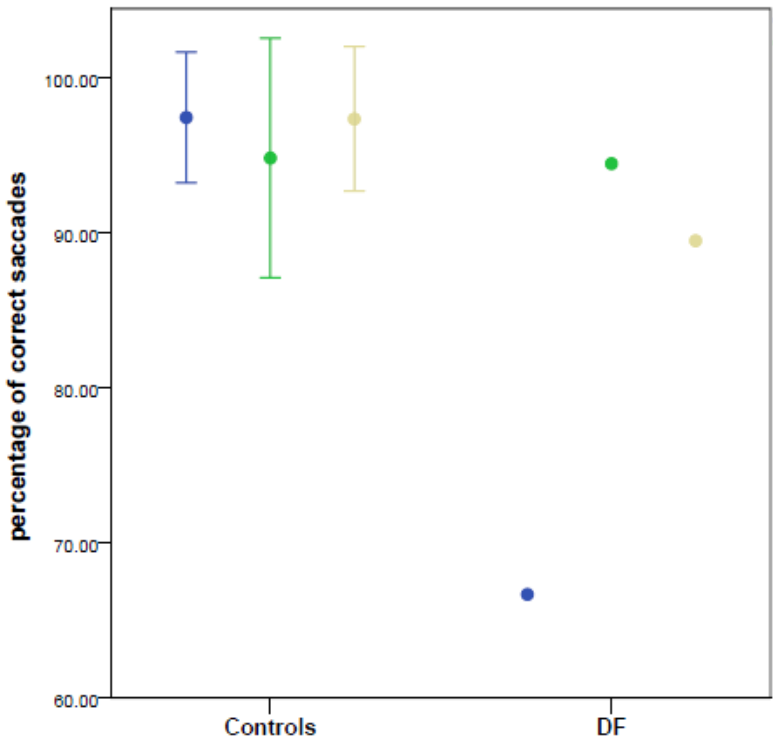


Fig. 4.4: Percentage of correct saccades for controls (N=6; means with 95% confidence interval) and DF for the memory-guided, delayed condition for left (blue), centre (green) and right (yellow) targets.

[1] When excluding this subject a clear impairment for DF was revealed on the right also [$t_{(4)}$=-3.5, p<.01]

Table 4.5: Percentage of correct saccades for controls (N=6) and DF for the memory-guided, delayed line condition for left, centre and right targets.

		Controls	Patient DF
Left	Stimulus-driven	100	100
	Memory-guided	97.4 (SD 4)	66.7
Centre	Stimulus-driven	99 (SD 2.2)	100
	Memory-guided	94.8 (SD 7.4)	94.4
Right	Stimulus-driven	98 (SD 2.8)	100
	Memory-guided	97.3 (SD 4.4)	89.5

Furthermore, I looked at the difference score between the stimulus-driven and the memory-guided condition (for a description of this score please see 3.2.2.1). Control participants showed small differences between the two conditions [1.6% (SD 5.3), 4.3% (SD 8.4) and 0.2% (SD 5.5) for left, centre and right stimuli] indicating that their performance on stimulus-driven saccades was just slightly better. DF showed difference scores of 33.3%, 5.6% and 10.5% for left, centre and right lines (table 4.6). As before the t-tests showed that she was significantly impaired on the left [$t_{(5)}$=5.5, p<.001] when compared to the age-matched controls' performance, but there was again only a trend for a deficit on the right [$t_{(5)}$=1.7, p>.072] [2]. Moreover, DF's difference score was significantly greater for the two lateral targets [left and right combined, ($t_{(5)}$ = 3.7, p<.01)] compared to the score of the control sample. These greater differences between the two conditions in DF indicate a much greater impairment for the memory-guided saccades towards the laterally presented stimuli, when compared to the stimulus-driven saccades. However, she showed no increased impairment for memory-guided saccades towards centrally presented stimuli compared to the stimulus-driven saccades (fig. 4.5).

[2] It is worth noting that the lack of effect was driven by the same control participant that I excluded earlier, and his exclusion revealed a significant effect of right target also [$t_{(4)}$=4.6, p<.01].

Table 4.6: Difference in percentage between the two experimental conditions (calculated as percentage of correct delayed saccades minus percentage of correct immediate saccades) for controls (N=6) and patient DF for left, centre and right targets.

	Controls	Patient DF
Left	1.6 (SD 5.3)	33.3
Centre	4.3 (SD 8.4)	5.6
Right	0.2 (SD 5.5)	10.5

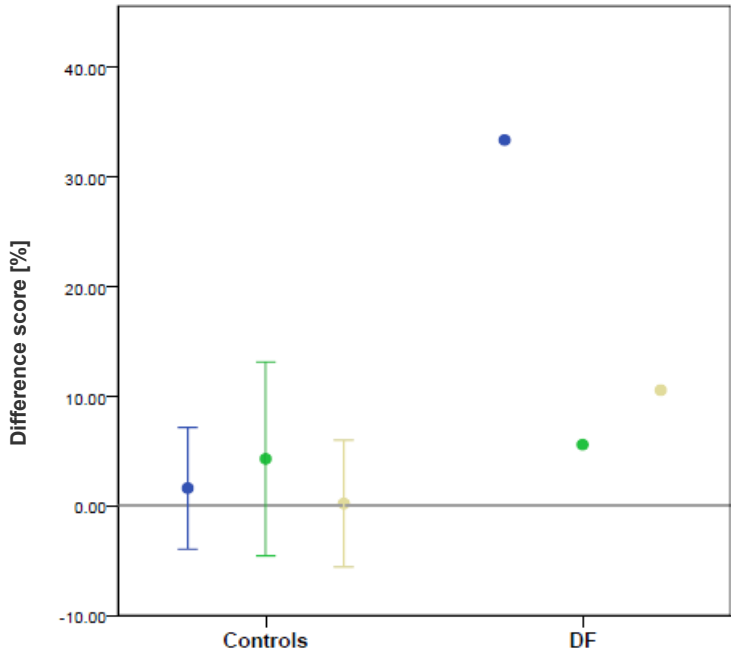


Fig. 4.5: Difference between the two experimental conditions (calculated as percentage of correct delayed saccades minus percentage of correct immediate saccades) for controls (N=6; means with 95% confidence interval) and patient DF for left (blue), centre (green) and right (yellow) targets.

4.3.2.2. Saccadic Reaction Time of first saccade

The t-tests on the saccadic reaction times for the stimulus-driven condition revealed no significant differences between DF and the controls although her saccades seemed a little slower for left and centrally presented stimuli with 353 ms, 369 ms and 295 ms for

leftwardly, centrally and rightwardly presented stimuli. The mean SRTs of the controls were 313 ms (SD 56.1), 312 ms (SD 40.9) and 294 ms (SD 32.8) (table 4.7).

For the memory-guided saccades, healthy controls showed a mean reaction time of 467 ms (SD 35), 430 ms (SD 60) and 427 ms (SD 50.6) for left, central and right lines, respectively, while DF showed reaction times of 556 ms, 505 ms and 530 ms. The t-tests showed that her performance was significantly slower than that of the age-matched controls for both left and right targets [$t_{(5)}$=2.3, p<.05 and $t_{(5)}$=2, p<.05 respectively], while no difference between DF and the controls occurred for the central stimuli (table 4.7).

Table 4.7: SRT in ms of healthy controls (N=6) and patient DF's for left, centre and right stimuli for the stimulus-driven and the memory-guided condition.

		Controls	Patient DF
Left	**Stimulus-driven**	313 (SD 56.1)	353
	Memory-guided	467 (SD 35)	556
Centre	**Stimulus-driven**	312 (SD 40.9)	369
	Memory-guided	430 (SD 60)	505
Right	**Stimulus-driven**	294 (SD 32.8)	295
	Memory-guided	427 (SD 50.6)	530

4.3.3. Discussion

Regarding the delayed performance, the data indicate that dorsal stream structures, which are mostly intact in DF, may not be sufficient to drive accurate and timely memory-guided saccadic performance and that the ventral stream may have to be involved as well. In fact, a recent TMS study by Cohen et al. (2009) has made very similar arguments regarding cortical involvement in delayed grasping. To tease apart the contribution of specific areas within the dorsal and ventral streams to the control of grasping under immediate and delayed conditions, they applied TMS both to the

anterior IPS and to the LO cortex. Most interestingly they showed that while TMS to the anterior IPS affected grasp under both immediate and delayed conditions, TMS to LO influenced grasp only under the delayed conditions. The authors conclude that the anterior IPS may be storing some (see also similar results by Himmelbach et al., 2009), but not all of the information necessary to control delayed actions, so that both anterior IPS and LO are required, with the LO almost certainly playing a role in the perceptual memory representations of the target location. To my knowledge, no-one has yet investigated LO's involvement in memory-guided saccades with TMS but a similar result might be expected.

Yet, there is also clear evidence from single-unit electrophysiology in the macaque (Gnadt & Anderson, 1988; Barash et al., 1991), as well as from brain imaging and TMS studies in the human (Schluppeck et al., 2006; Schluppeck, Glimcher & Heeger, 2006; Nyffeler et al., 2005), that the PPC is activated during memory-guided saccade processing. This area (on the right in particular, she has a very small left PPC lesion) is spared in DF (James et al., 2003), yet accuracies and latencies to both left and right stimuli were compromised for her. I would argue that although dorsal stream structures are clearly involved in memory-guided saccadic processing, they may not be sufficient to drive accurate and timely memory-guided saccadic performance.

I suggest instead, in line with the predictions from Milner and Goodale's model that the ventral stream, which represents an object long-term, has to be functional to allow accurate memory-guided saccade processing. This extends Milner and Goodale's arguments about the timing of the two streams to the oculomotor domain. In fact, similar results had been found in a preliminary study carried out by Dijkerman and colleagues on DF some years earlier (Dijkerman, Milner & Carey, 1997). They used a quite different (linear) stimulus array and varied eccentricity, yet also found that,

compared to two controls, DF was much worse in the delay condition. The agreement between the results further adds to their credibility.

Although DF's greatly reduced accuracy and increased latencies for memory-guided eye movements and her ability to execute stimulus triggered saccades in the immediate condition are in line with predictions from Milner and Goodale's model (1995; 2006), the exceptions to this pattern of impairment were her memory-guided saccades to the centrally presented stimuli. As the N+ patients I tested with the same task (chapter 3.2) were clearly impaired for centre lines, it is very likely that DF may have used coping strategies like using the monitor screen as an on-line egocentric reference, or she could have used the fixation dot, which remained present during the delay period, as a positional cue and/or even simply verbally rehearsed 'centre' over the delay period. Alternatively, she might have verbally recoded the stimulus as 'up, down, left or right'. Again this would help her for the central stimuli but not the others. As the control subjects were virtually at ceiling for both the stimulus triggered and delayed conditions, I cannot be certain about these explanations, yet they seem the most parsimonious.

Moreover, DF seemed to have greater problems in saccading to leftwardly memorised targets than to remembered locations on the right (in fact there was a trend only when all subjects were included). Beside her strabismus, one could also speculate that this may be related to the fact that her ventral stream lesion is more extensive in the right hemisphere compared to the left (James et al., 2003). In my view, this finding is worth exploring further as most studies on DF do not present results, or even test experimental designs, separately for left and right space. This might be because it is assumed that the bilateral ventral stream lesions will yield symmetrical results.

Finally, as outlined in the introduction, it has been shown repeatedly that DF is normal in immediate reaching and grasping, yet severely affected when asked to

perform delayed actions. I have further found here that she can execute stimulus triggered (immediate) saccades yet is impaired in memory-guided (delayed) ones suggesting a tight coupling of hand and eye movements.

To summarise my findings, just as reported for reaching and grasping, I found that DF's saccadic performance was compromised in the memory compared to the stimulus-driven saccade condition. I thus argue that the visual dorsal stream may not be sufficient to drive successful memory-guided saccadic performance but that, in line with Milner and Goodale's (e.g. 1995; 2006; 2008) model, an intact visual ventral stream is also necessary.

4.4. Experiment 3: Oculomotor on-line correction

Finally, having largely focused on ventral stream (off-line) performances in the first two experiments, in a third experiment I will test whether DF performs normally in saccadic on-line corrections. The task will involve saccading towards simple stationary targets that are interleaved with trials in which the targets suddenly changes position. In the latter trials, DF is required to follow the perturbed target. Please see chapter 3.3 for a detailed description of the task.

DF has previously shown that she can interact perfectly with presented targets. She was able to adjust her grasp well in advance of target contact for example (Carey, Harvey & Milner, 1995) and even when she picked up objects of random shapes (Goodale & Humphrey, 1998) she did not differ from healthy participants, which is in agreement with her intact dorsal stream function. As described in chapter 3, various studies have found evidence that the PPC, which is believed to be part of the dorsal stream (e.g. Milner & Goodale, 1995), is involved in on-line control (e.g. Grea et al., 2002). Indeed, optic ataxia patients, who frequently have a PPC lesion, are often impaired when they have to interact with targets in real-time (e.g. Goodale & Humphrey, 1998). Moreover, compared to healthy participants they often adjust their movements towards a perturbed target only slowly (e.g. Grea et al., 2002; Blangero et al., 2008).

With her small PPC lesion yet mostly spared dorsal stream, I therefore expect patient DF not only to be capable of saccading towards stationary targets but also to perform saccadic on-line corrections towards suddenly moving targets. Thus her performance should be similar to the previously reported neglect patients (chapter 3.3).

4.4.1. Method

Healthy participants

The same six healthy control subjects as in the memory-guided saccades experiment (chapter 4.3) were chosen to be age matched controls to patient DF.

Patient DF

For a detailed description of patient DF, please see chapter 4.2.

Apparatus, stimuli, data processing and procedure

Apparatus, stimuli, data processing and procedure were identical to the previously described study (see chapter 3.3.1). However, instead of three blocks with 60 trials each, patient DF completed six blocks while the control subjects completed three blocks only.

The exclusion criteria of too short latencies, improper fixation and too small saccade amplitudes resulted in a rejection of 15% for the no-jump trials for the healthy controls and 27.4% for DF. For the jump trials, these numbers were 14.2% and 29.6% respectively. For a detailed list of the amount of excluded trials please see table 4.8.

Table 4.8: Percentage of excluded trials for the anticipation, fixation and amplitude criteria, for no-jump and jump trials, presented separately for controls and DF.

		No-Jump	Jump
Controls	**anticipation**	5.8%	4.9%
	fixation	7.9%	7.1%
	amplitude	1.7%	2.2%
DF	**anticipation**	4.9%	3.7%
	fixation	7.1%	19.4%
	amplitude	2.2%	6.5%

4.4.2. Results

To test whether DF's performance differed from the control sample I used the modified t-test (Crawford and Howell, 1998), which has been developed specifically to compare the performance of a single patient to the results obtained from a sample of age-matched controls. As DF has repeatedly shown a clear impairment for off-line performances while she was not impaired for on-line tasks, I expected her to be unimpaired for on-line corrections. Therefore the one-tailed p-value for the results was used. For the analyses I used the same variables as described previously (see 3.3.2). Please see table 4.9 for a summary of DF's data.

4.4.2.1. No-Jump

Regarding the absolute angular error of the first saccade in the no-jump trials a difference was found between DF and the healthy controls. With a mean absolute angular error of 4.19 degrees, DF accuracy was significantly worse compared to the healthy controls whose angular error was 1.85 degrees (SD 0.4) [$t_{(5)}$=4.9, p<.01]. Nevertheless, the accuracy of the control participants and patient DF seemed to be reduced with most saccades falling too short and furthermore with a slight tendency to the right side for DF (fig. 4.6).

No difference between DF and the control subjects was found for the saccadic reaction time with DF only performing slightly slower than the healthy participants (DF: 341 ms; controls: 261 ms, SD 39.5).

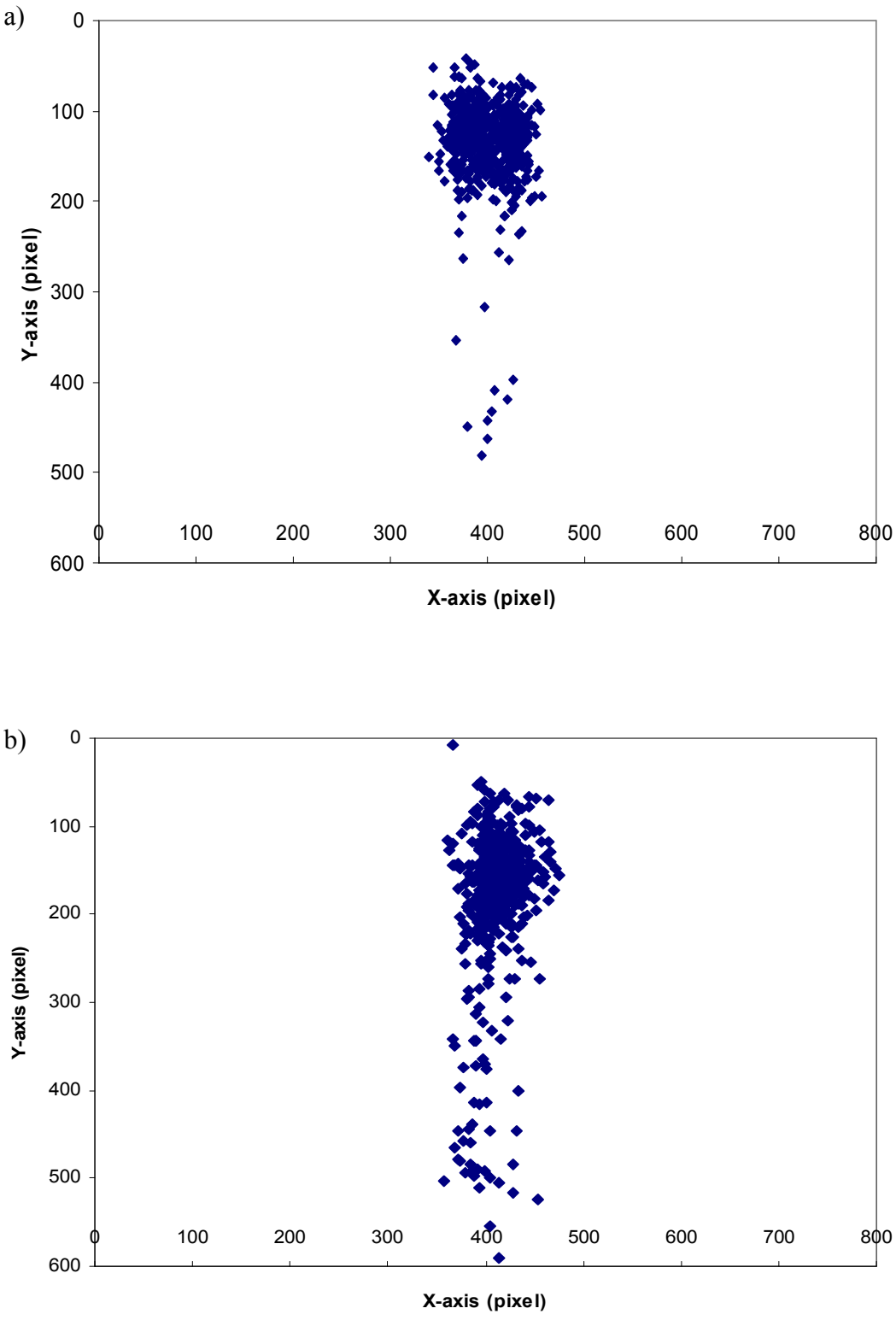


Fig. 4.6: Individual landing points of first saccade in no-jump trials of the control participants (a) and patient DF (b); target located at position 400,100.

4.4.2.2. Jump

Looking at the jump trials, no difference was found between DF and the healthy participants regarding the absolute angular error of the most accurate saccade for right and left target jumps. DF was able to adjust her eye movements to the suddenly changing target location like the controls (absolute angular error: DF 1.04 degrees for left and 0.66 degrees for right targets; controls 0.94 degrees, SD 0.4 for left and 0.87 degrees, SD 0.3 for right targets).

The t-tests on the number of saccades that were needed to reach the most accurate saccade, revealed significantly more saccades for DF for right target jumps (2.7 saccades) compared to the healthy controls (2.1 saccades; SD 0.3) [$t_{(5)}$=2.2, p<.05]. No difference between DF and the controls was found for the number of saccades needed for left target jumps (DF: 2.9; controls: 2.2, SD 0.3). Beside the increased number of saccades for right jumps I also found significantly longer cumulative saccadic reaction times for right targets, with DF taking significantly longer to reach the most accurate saccade compared to the healthy participants (DF: 713 ms; controls: 468 ms, SD 78.6) [$t_{(5)}$=2.9, p<.05]. No latency difference was found for left target jumps. Here DF did not take longer to reach the smallest absolute angular error than the controls (DF: 693 ms; controls: 521 ms, SD 86).

Table 4.9: Absolute Angular Error (in degrees), number of saccades and SRT of healthy controls and patient DF's no-jump and jump trials (separately for left and right jumps).

		Controls	Patient DF
No-Jump	**Absolute Angular Error** [degrees]	1.85 (SD 0.4)	4.19
	Saccadic Reaction Time [ms]	261 (SD 39.5)	341
Jump	**Absolute Angular Error Left** [degrees]	0.94 (SD 0.4)	1.04
	Absolute Angular Error Right [degrees]	0.87 (SD 0.3)	0.66
	Number of Saccades Left [ms]	2.2 (SD 0.3)	2.9
	Number of Saccades Right [ms]	2.1 (SD 0.3)	2.7
	Saccadic Reaction Time Left [ms]	520 (SD 86)	693
	Saccadic Reaction Time Right [ms]	468 (SD 78.6)	713

4.4.3. Discussion

I found evidence previously that patient DF performed well on stimulus-driven, immediate saccades while she was impaired in the memory-guided condition (chapter 4.3). In this experiment I now examined DF's capability to correct stimulus-driven saccades towards targets that suddenly changed its location. The results show that she performs well in the task and can execute on-line corrections like the healthy control group. No difference was found regarding the absolute angular error which shows that her saccades are as accurate as the saccades executed by the control group.

These results are in line with predictions from Milner and Goodale's model (e.g. 1995; 2006), which states that the dorsal stream works in real-time for immediate use in guiding actions. According to DF's lesion (James et al., 2003), her dorsal stream (with the exception of a small left PPC lesion) remains intact which explains her ability to perform on-line corrections. My results also give further evidence for a double dissociation: While DF has repeatedly shown that she is able to act to presented targets and I show here that she can perform on-line corrections, optic ataxia patients are

impaired on these tasks. It has been reported that in pointing tasks they need a greater number of arm movements to reach a suddenly jumping target dot compared to healthy controls (Grea et al., 2002). Also, optic ataxia patients seem to prefer the use of memorised information about a target to complete a task (Milner et al., 1999; Milner et al., 2001), while DF shows worse performance in memory-guided compared to stimulus-driven actions (e.g. Dijkerman, Milner & Carey, 1997; Rossit et al., 2010; chapter 4.3). Moreover, DF shows comparable results for pointing (Dijkerman, Milner & Carey, 1997; Carey et al., 2006) and oculomotor behaviour (Rossit et al., 2010; chapter 4.3) with more accurate responses in stimulus-driven conditions compared to delayed tasks.

However, it is important to mention that, although DF was able to carry out accurate on-line corrections, she showed unexplainable longer latencies for right target jumps and a greater number of saccades towards right targets compared to the control group. Her small left PPC lesion might possibly drive this asymmetry. Nevertheless, she also needed slightly more saccades for left target jumps compared to right target jumps (2.9 saccades and 2.7 saccades respectively) and her absolute angular error for left targets was greater than for right targets (1.04 degrees and 0.65 degrees respectively) but none of these results differed from the healthy controls.

Furthermore, for unperturbed target trials I also found that DF, like the stroke patients, showed a tendency to slightly saccade to the right side instead of straight upwards. Moreover, DF performed worse than her age-matched controls in the no-jump trials but again I found that she was able to reach the target accurately when more saccades than only the first one were considered. Like I reported in the previous discussion on stroke patients (chapter 3.4) the control participants also showed a slightly greater absolute angular error for no-jump trials compared to the jump trials, thus suggesting that the experimental design affected the performance of all participants and

in particular the patients. (See also section on design issues in the discussion of chapter 3 for further limitations of the interpretation)

To summarise my findings, the results of this experiment are in line with Milner and Goodale's model (e.g. 1995; 2006) which predicts that stimulus triggered saccades are supposed to be driven by dorsal stream structures. These areas are thought to be relatively spared in patient DF (James et al., 2003). Unlike optic ataxia patients who show greater problems in stimulus-driven actions and on-line corrections in particular, DF can indeed perform ocular on-line corrections. Therefore I conclude that these results provide further evidence for the PPC, which is part of the dorsal pathway, being involved in visual-guided action and on-line corrections.

4.5. General conclusions

Previous studies on patient DF have repeatedly reported that she is able to perform on-line actions like pointing towards visible targets for example (e.g. Carey et al., 2006) while she is impaired in off-line performances like delayed grasping (e.g. Goodale, Jakobson & Keillor, 1994). These results are in line with Milner and Goodale's model (e.g. 1995; 2006) that the visual dorsal stream processes actions in the here and now (on-line) and the visual ventral stream is involved when target characteristics has to be maintained over time for delayed actions for example (off-line). Indeed, lesion analysis revealed that DF's dorsal stream remains intact while her ventral stream is effected (James et al., 2003). Conversely, patients with optic ataxia after dorsal stream lesions, paradoxically improve for off-line actions when the response is delayed for example and the target object has been removed from view (e.g. Milner et al., 1999; 2001).

A series of three tasks was now conducted to find further evidence for the dorsal- ventral stream dichotomy and most importantly to extend the previous findings by using oculomotor tasks as, so far, DF has been tested almost exclusively on pointing or grasping tasks. In line with previous results, DF was again impaired for most of the off-line tasks (anti-saccades and delayed, memory-guided saccades) while she showed no major deficits for on-line tasks (pro-saccades, immediate saccades and on-line corrections). Furthermore, DF's perfect fixation performance supported the assumption that her anti-saccade errors were indeed rather caused by an inability to remap the target location to the opposite side, i.e. to perform an off-line action, than an inhibition failure, as this would have resulted in erroneous pro-saccades, which did not occur for the fixation or the anti-saccade trials. Instead her anti-saccade errors consisted of a decreased saccade accuracy.

Finally, as my findings agree with previous reaching and grasping results on DF, I assume that they can be taken as evidence for a tight coupling of hand and eye movements.

Critical evaluations of the task designs and its possible constraints regarding interpretation have been discussed previously in chapters 2 and 3 when I reported the data for the stroke patients I tested, and I will elaborate on these in the general discussion.

Chapter 5

GENERAL DISCUSSION

5.1. General aim of the thesis

This thesis was conducted to examine the oculomotor on- and off-line behaviour of neglect patients and visual form agnosia patient DF to establish whether Milner and colleagues' (Milner & Harvey, 2006) action dichotomy can be extended into the oculomotor domain. A lot of evidence for Milner and Goodale's dichotomy (1995; 2006), i.e. that the visual dorsal stream works in real time for immediate use to guide on-line actions, and the visual ventral stream allows object characteristics to be maintained over time for off-line tasks, comes from patient DF. Patient DF has lesions to her ventral stream while her dorsal stream remains largely intact (James et al., 2003). In line with predictions from Milner and Goodale's model (1995; 2006; 2008), she is impaired for off-line tasks like delayed actions (e.g. Goodale, Jakobson & Keillor, 1994; Dijkerman, Milner & Carey, 1997) while she has no problems to perform on-line tasks such as pointing towards targets or target sequences (e.g. Carey et al., 2006).

More recently, studies on patients suffering from hemispatial neglect also support the argument that on-line and off-line tasks depend on different cortical networks. Rossit et al. (2009b; 2011) have found dissociations between on- versus off-line actions in neglect patients, arguing that the visual dorsal steam is relatively spared in these patients and that this mediates the spared on-line reaching and grasping, whereas the impaired off-line actions are the result of damage to the superior and middle temporal lobes. Although these areas are outside the visual ventral stream, the authors argue that they have ventral stream like properties also.

Yet all studies that have been done on neglect patients so far and most of the studies on DF, have used pointing and grasping tasks. Therefore, I designed a series of tasks to examine the possibility if the previously found functional differences between on- and off-line tasks may also be found for oculomotor tasks. Although DF has

confirmed lesions to the ventral stream (James et al., 2003) the heterogeneity of the lesions in patients with hemispatial neglect, makes an anatomical argument much more difficult. Therefore, my aim was to discuss performance differences mostly on a functional, rather than anatomical level.

My first experiment focused on a previous study by Butler et al. (2009) that described anti-saccade failures in neglect patients. Using a simple fixation task that was carried out in addition to Butler et al.'s pro- and anti-saccade conditions (chapter 2.2) as well as a more complex interleaved fixation and pro-saccade task (chapter 2.3), my aim was to determine, whether the erroneous pro-saccades found in the anti-saccade condition were caused by an inhibition failure. I argued that, if the patients were able to withhold saccades in the fixation trials, the anti-saccade errors could possibly be the result of a remapping problem and thus in line with predictions that neglect patients are impaired for off-line actions. Furthermore, the task was also carried out with patient DF and the same results as for the neglect patients were expected, as she has previously shown anti-saccade and other off-line task deficits (Dijkerman, Milner & Carey, 1997; Carey et al., 2006).

Next I tested on-line and off-line actions with an immediate and delayed saccadic task (chapters 3.2 and 4.3). In line with previous results (e.g. Goodale, Jakobson & Keillor, 1994; Rossit et al., 2009b), I expected DF and the neglect patients to be unimpaired in the immediate saccades (on-line action), while I predicted a deficit in the delayed saccades (off-line task).

Finally I tested the ability to perform oculomotor on-line corrections towards perturbed targets (chapter 3.3 and 4.4). McIntosh et al. (2010) already reported that, in a reaching task, automatic on-line corrections were not impaired in patients with hemispatial neglect. Patient DF has repeatedly shown perfect performance for on-line

tasks. Therefore I expected the ability to perform oculomotor on-line corrections to be relatively spared in both neglect patients and DF.

All tasks, except the interleaved fixation and pro-saccade task (chapter 2.3), were carried out on both neglect patients and patient DF. Also, for all tasks, except the first anti-saccade, pro-saccade and fixation task (chapter 2.2) an additional stroke patient group without neglect was tested to serve as an additional control group to the neglect group (in addition to the healthy control group).

The main findings of the tasks will be summarised in the following section.

5.2. Overall findings and evidence for dissociations between oculomotor on- and off-line actions

The tasks I conducted were designed to compare on-line versus off-line actions as various studies have found evidence for a functional dissociation linked to different cortical networks. I found this functional dissociation with my tasks too: most of the neglect patients and patient DF were able to perform the on-line tasks while they were impaired for the off-line tasks. The on-line tasks that I used in my thesis were pro-saccades (chapters 2.2, 2.3 and 4.2), immediate saccades (chapters 3.2 and 4.3) and on-line corrections (chapters 3.3 and 4.4).

Oculomotor on-line actions in hemispatial neglect

The results for the neglect patients showed that they never failed to saccade in the blocked pro-saccade condition (chapter 3.2). The patients saccaded to both, left and right, target positions. I found neglect typical leftward biases with slightly longer latencies and greater inaccuracy to left targets and neglect typical behaviour was also found for the pro-saccades in the interleaved task (chapter 3.3). Yet as most of the patients were able to saccade accurately towards right targets and executed leftward

saccades, I would argue that this leftward impairment can be seen as a neglect typical failure and not as an on-line deficit.

The next task that involved on-line performance required immediate saccades towards lines (chapter 3.2). Here the participants were asked to saccade towards a line that could point to one of six possible directions (as quickly as possible when the line appeared). As expected, the neglect patients had no problems to execute accurate and fast eye-movements towards each line. Their performance did not differ from the patient control group although they performed slightly worse than the healthy control group.

Finally, the on-line correction task (chapter 3.3) required the patients to saccade towards a target that could suddenly and unpredictably change its location. In these perturbed trials, the participants had to adjust their eye-movements and follow the target. Again, most of the neglect patients were able to correct their saccades in these perturbed trials. Furthermore, failures to perform this on-line correction task were often connected to parietal lobe lesions, which might involve the visual dorsal stream. These findings are in line with previous studies on patients with optic ataxia, a condition that frequently occurs after damage to the PPC which is part of the dorsal stream. These patients are impaired for on-line correction tasks (Grea at al., 2002; Gaveau et al., 2008; Goodale, Jakobson & Keillor, 1994).

Oculomotor off-line actions in hemispatial neglect

In contrast to a simple pro-saccade, in the anti-saccade condition (chapter 2.2), the target location has to be remapped to the opposite side. Here the neglect patients were clearly impaired and the percentage of correct anti-saccades was very low with a large number of erroneous pro-saccades generated to both sides. This behaviour was very different from the rather subtle neglect typical biases observed for the pro-saccades. The patients clearly showed a general failure to find the correct mirrored location. I

speculated that this failure could either be the inability to perform off-line actions in general, i.e. to perform a vector inversion and remap the target location to the opposite side, or a problem to inhibit saccades towards the target (see also Butler et al., 2009). With an additional fixation task, I therefore narrowed the possible reasons for the anti-saccade deficit by allowing an assessment of the neglect patients' ability to inhibit stimulus driven saccades. The results showed that no general inhibition impairment could be found for the neglect patients. Similar results were found for the more complex inhibition task (chapter 2.3). I thus concluded that the anti-saccade errors are possibly not caused by inhibition problems but rather by an off-line deficit i.e. to remap the target location to the opposite side. I have to concede that this argument is rather indirect as in the end, I tested only five neglect patients directly on the anti-saccade task.

The second off-line task I designed was the oculomotor memory-guided task. Here I found the expected impairment for the delayed performance for the neglect patient group, with many errors in the memory-guided condition compared to the healthy controls. Furthermore, the performance detriment between the immediate and the delayed condition was much greater than that shown for the controls. However, no difference was found between the N+ and N- group and although this may have been due to lack of power (see Limitations of patient testing below) this impairment may not be neglect specific. Finally, spatial working memory impairments could also account for the failure in this task (see chapter 3).

Patient DF

Apart from the neglect patients, I had the chance to test visual form agnosia patient DF on these on- and off-line tasks. As expected, DF showed no general problems to perform the on-line tasks pro-saccades (4.2), immediate lines (4.3) and on-line corrections (4.4). On the other hand, also as predicted, she was impaired for the off-line

tasks anti-saccades (4.3) and delayed lines (4.3). Like the neglect patients she was not impaired in the additional fixation condition (4.2), thus I would argue that her anti-saccade failure is an off-line remapping deficit, an assumption that is in line with previous findings that have demonstrated that she is impaired in off-line actions (e.g. Dijkerman, Milner & Carey, 1997; Goodale, Jakobson & Keillor, 1994; Carey, Harvey & Milner, 1996).

DF has been tested repeatedly on on- and off-line tasks and my findings support previous results showing that she is able to perform on-line tasks while she is impaired for off-line actions. I was able to extend these previous findings on pointing and grasping with a series of oculomotor tasks. As she has confirmed lesions to the ventral streams while her dorsal stream remains largely intact (James et al., 2003), the results are also in line with Milner and Goodale's (e.g. 1995; 2006; 2008) dorsal- and ventral-stream model, according to which on-line and off-line actions involve different brain structures.

On the other hand, the lesions in my neglect patients varied greatly and I am thus almost unable to make anatomical inferences from them. On a functional level the neglect patients in my study were similar to patient DF, although neglect typical deficits occurred occasionally, for example in the pro-saccade task. Neglect often occurs after lesions to the IPL (Vallar & Perani, 1986; Mort et al., 2003) and the STG (Karnath, Ferber & Himmelbach, 2001; Karnath et al., 2004) and indeed Milner and Goodale (1995) speculate that the IPL gets input from ventral stream areas. Furthermore, Rossit et al. (2009a) found that the delayed pointing deficits in their neglect patients were connected to damage to the superior and middle temporal gyri. Although some of my patients had similar lesions and I discuss this in chapter 3, I simply did not manage to test enough patients with these types of lesions to confirm that these structures are involved in oculomotor off-line tasks too (see also Limitations of patient testing)

Further limitations regarding participant group and experimental design that apply to this thesis and that might have interfered with the results, will be discussed in the following sections.

5.3. Limitations of patient testing

One major problem that occurs when conducting patient studies is the often small number of suitable participants. As said before, on a functional level I did find differences between on-line and off-line tasks for neglect patients. Yet, I had aimed to find evidence for the IPL, STL and middle temporal lobes, which are frequently damaged in neglect patients (Karnath, Ferber & Himmelbach, 2001; Mort et al., 2003), to be involved in off-line oculomotor control, to allow me to extend previous findings on on- and off-line grasping and pointing tasks (e.g. Rossit et al., 2009b) into the oculomotor domain. However, the lesions of the patients that participated in my study varied greatly and most patients did not have the hoped for lesions to the IPL or superior or middle temporal lobes. Thus, unfortunately I cannot draw any firm anatomical conclusions.

Also it has to be taken into account, that other factors like current medication or associated conditions such as depression or fatigue might interfere with the ability to perform experimental tasks. Singh-Curry and Hussain (2009) have argued that the IPL is crucial for a fronto-parietal network that is involved in attention (for example sustained attention), which is necessary for successful task performance. Various studies have further reported a contribution of the frontal and parietal lobes as well as subcortical structures to attentional tasks (e.g. Adler et al., 2001; Corbetta & Shulman, 2002; Hager et al., 1998; Lawrence et al., 2003; Luks et al., 2008; Sturm et al., 1999; Vandenberghe et al., 2001). For example Lawrence et al. (2003) found a correlation

between good performance in a sustained attention task and activation in the right fronto-parietal region. Moreover, Malhotra, Coulthard and Husain (2009) tested neglect patients and reported that the right PPC is involved in sustaining attention to spatial locations.

As the lesions of my stroke patients varied greatly, I can assume that these other deficits, regardless of the presence of neglect, could have interfered with the performance of both patient groups, which could also explain the absence of neglect specific differences.

Finally the small number of participants in each patient group (between five and seven N+ and five or six N- patients, depending on the particular experiment) resulted in low statistical power. I had hoped to find between subjects effects for the independent variable *group,* with neglect patients being more impaired than the healthy controls and no-neglect patients. I found that neglect patients were more impaired than the healthy controls but although they appeared to show greater problems than the no-neglect patients also, this difference was not significant. The small patient groups and thus the low power of the tests might have prevented these differences to become apparent and therefore deficits that appeared to be not neglect specific might have been neglect specific.

Crawford and Howell's modified t-test (1998) that was designed to compare one participant to a larger group was used to test if individual patients were impaired. Yet as mentioned earlier, the lesions of my patients varied too much and very often more than one brain area was affected by the stroke, which made any conclusions difficult. Testing larger groups of patients, particularly with lesions to the IPL or superior or middle temporal lobes would be necessary to firm up my present results.

5.4. Experimental limitations and future studies

Apart from the above mentioned limitations that come with small participant groups, I will now take a critical look at the experimental designs of my tasks to discuss if the chosen tasks were in fact appropriate to examine oculomotor on- and off-line actions. Furthermore I will suggest task changes where limitations of the current experiments were identified and outline future studies also.

Anti-saccades, pro-saccades and fixation (chapters 2.2, 2.3 & 4.2)

The first experiment (chapters 2.2 and 4.2) was a follow up study to Butler et al.'s study (2009). Butler and his colleagues found that neglect patients were impaired in executing right and left anti-saccades and instead produced a large number or erroneous pro-saccades. Therefore my experiment consisted not only of anti-saccades and pro-saccades but also contained an additional block of fixation trials. The block with fixation trials was conducted to determine whether the erroneous pro-saccades were caused by an inhibition problem or the inability to remap the target location to the opposite side (off-line performance). I replicated Butler et al.'s findings of erroneous pro-saccades to right and left targets, and furthermore most patients were able to inhibit eye-movements in the fixation block and also in a more complex inhibition task (chapter 2.3).

Therefore I suggested that the erroneous pro-saccades were not the result of an inhibition problem but were more likely an off-line remapping deficit. However, although the simple and more complex inhibition tasks in chapter 2 were designed to shed light on the underlying anti-saccade (off-line) problems some questions remain open. So far my results can simply exclude inhibition problems as a cause for anti-

saccade deficits but I need more evidence to show that the impairment is indeed a remapping problem.

This could be done by varying the target location and using more than two locations. It could be argued that if patients have problems to perform anti-saccades in a task where the target appears at only two possible locations, they might be even more impaired when more target locations are used. However, the targets in my experiment were presented on a horizontal line and for the left target, the anti-saccade endpoint fell into the neglected field of the patients. Indeed most pro-saccades towards left targets were very inaccurate (chapters 2.2 and 2.3) and for the more complex, interleaved task (chapter 2.3) frequent omissions occurred for some of the N+ patients. Thus the deficits in my anti-saccade task could be driven by neglect typical behaviour during target detection and/or saccade execution. To control for these factors it would be necessary to present targets at other locations, i.e. at different locations around the central fixation point, at different distances from the fixation point and including vertical target presentation. If the errors persist, this would give much greater support to the idea of an off-line remapping failure. These experiments should be run on patient DF also and I have in fact collected this data on her. A preliminary analysis has shown that she can perform anti-saccades to more than simply two horizontal locations.

The addition of an N- patient group would further help establish if the erroneous pro-saccades in the anti-saccade task were neglect specific or not.

Delayed and immediate oculomotor performance (chapter 3.2 & 4.3)

The delayed and immediate line task was designed to compare on- to off-line performances. However, although both tasks used the same stimuli and array, the differences between the conditions cannot be ignored. Firstly, the different stimulus presentation times can be seen as a possible weakness of the tasks. While the line was

present for 1,000 ms in the immediate condition, it appeared for 200 ms only in the delayed condition. Thus a comparison is not ideal and a necessary follow up study on both neglect patients and DF would have to equate presentation time for a start. A further problem with the current design arises from the fact that the stimulus was present when a saccade was made in the immediate condition, yet absent in the delayed condition. It is necessary to replicate this study with a design in which the visual stimulus would be absent from both conditions at the time of saccade onset.

It would also be really interesting to adapt the Cohen et al. (2009) experiment to an improved version of this task. To recap, Cohen and colleagues applied TMS during immediate and delayed grasping tasks over dorsal and ventral stream structures, namely the anterior IPS and the LO cortex respectively. They found that TMS over the LO caused deficits in delayed action. Furthermore, TMS over the anterior IPS resulted in impaired performance in immediate and delayed trials. If these findings could be replicated for my (improved) oculomotor task, that would provide strong corroborating evidence that immediate and delayed saccades are also mediated by different cortical networks.

Oculomotor on-line corrections (chapter 3.3 & 4.4)

While the pro-saccade and immediate saccade tasks were designed to find evidence for both neglect patients and patient DF to be able to perform oculomotor on-line tasks, the on-line correction task was used to examine a special form of on-line action, namely automatic corrections ("autopilot"). Previous studies have shown that automatic corrections towards targets that suddenly change its location are usually made in one smooth pointing movement (Grea et al., 2002) without participants actually detecting the change in target location. My oculomotor task was adapted from Pisella et al.

(2000), Blangero et al. (2008) and Rossit and Harvey (2008)'s pointing tasks to study automatic oculomotor behaviour.

Although I made a great effort to prevent the target jump from being detected by the participants, by placing the target at the greatest possible distance from the start point at the top of the screen and by triggering the target jump with saccade onset, most participants reported that they had seen the jump. It has to be acknowledged that Pisella et al's (2000) participants were also able to report the perturbation of a target. Yet, crucial evidence against my task testing the "autopilot" comes from the fact that, instead of one smooth corrective saccade, all participants needed more than one saccade to reach the target. Therefore I think my task probably failed to test an automatic corrective response and I suggest that the general experimental array has to be altered. It would be interesting to test if these problems occur also when target and start points are presented on a horizontal rather than vertical axis (see Gaveau et al., 2008).

Furthermore, it is possible that the distance between start fixation point and target was simply too big to be covered in one single saccade. In fact, most participants were able to reach the targets in the pro-saccade conditions (7.2 degrees for pro-saccades vs. 15.4 degrees for on-line corrections) in one eye-movement only (see chapters 2.2., 2.3. and 4.2.) and this would be an obvious easy improvement on the current design. Pisella et al. (2000) considered reaction times of 200-300 ms as automatic and although most of the first saccades that occurred in my task were indeed fast like this, more saccades were needed to reach both the stationary and perturbed target and this weakens my argument of the saccades having been automatic.

It also has to be taken into consideration that the task consisted of interleaved jump and no-jump trials. Because of this design, participants might have responded more carefully with the first saccade ending clearly below the target, to be able to adapt to a possible target jump (although they were told to respond as quickly as possible). I

thus suggest that presenting the target closer to the start point and/or presenting single blocks of jump and no-jump trials should result in an automatic response.

To further test if the response is automatic rather than voluntary, it would be interesting to test if participants would be able to stop when they detect a target jump. Pisella and colleagues (2000) have reported that the "autopilot", i.e. the corrective automatic response can hardly be overridden, once a hand movement towards a target has started. Most participants are simply unable to stop. Thus being unable to stop an oculomotor response when told to, would support an automatic design. (However, it might be impossible to stop an eye-movement once initiated, due to the greatly reduced inertia in the eye-movement system, I do not know this.)

5.5. Conclusion

In a series of oculomotor tasks I tested the on-line and off-line behaviour of neglect patients, stroke patients without neglect and visual form agnosia patient DF. DF's lesion involves ventral stream structures (James et al., 2003) and the IPL and the superior temporal lobes are most frequently damaged in patients suffering from hemispatial neglect (Karnath, Ferber & Himmelbach, 2001; Mort et al., 2003). Moreover, similarly to patient DF, previous studies have reported that neglect patients are impaired in off-line tasks while they show no deficits for on-line performances (Rossit et al., 2009b), which is in line with predictions from Milner and Goodale's model (1995; 2006; 2008).

On a functional level, my results support this distinction that has been established largely through the use of pointing and grasping tasks and I extend them to the oculomotor domain. The neglect patients, as well as patient DF, were impaired for the tested off-line actions anti-saccades (chapter 2.2 and 4.2) and delayed lines (3.2 and 4.3). At the same time, they were mostly able to perform pro-saccades (chapter 2.2 and

4.2), immediate saccades (chapter 3.2 and 4.3) and on-line corrections (chapter 3.3 and 4.4), i.e. on-line tasks. As the results show similar behaviour for the neglect patients and patient DF, I assume that the cortical networks involved are similar. While DF's ventral stream lesion is confirmed, the lesions in my neglect patients differed too much to allow me to come to a similar conclusion to Rossit et al. (2009a,b; 2011) who were able to link off-line action impairments to superior and middle temporal lobe lesions and argue that these areas have ventral stream properties.

The limited number of patients as well as the great diversity of brain lesions among the patients, made a prediction regarding involved brain areas impossible for me. More patients with lesions to brain areas of interest (particularly the IPL and superior and middle temporal lobes) are needed. Furthermore, the experiments that compared N+ and N- patients (e.g. delayed lines, chapter 3.2) failed to show a group difference, although the N+ patients still performed worse than the N- patients. Therefore, a larger patient group that includes neglect and no-neglect patients is needed also, as this would increase statistical power and shed light onto the question of neglect specificity for the reported off-line impairments.

References

Adler CM, Sax KW, Holland SK, Schmithorst V, Rosenberg L, Strakowski SM (2001). Changes in Neuronal Activation With Increasing Attention Demand in Healthy Volunteers: An fMRI Study. Synapse, 42, 266-272.

Amador N, Schlag-Rey M, Schlag J (2004). Primate Antisaccade. II. Supplementary Eye Field Neuronal Activity Predicts Correct Performance. Journal of Neurophysiology 91 (4), 1672-1689.

Barash S, Bracewell RM, Fogassi L, Gnadt JW, Andersen RA (1991). Saccade-Related Activity in the lateral intraparietal area. 2. Spatial Properties. Journal of Neurophysiology 66 (3), 1109-1124.

Barton JJS, Pandita M, Thakkar K, Goff DC, Manoach DS (2008). The relation between antisaccade errors, fixation stability and prosaccade errors in schizophrenia. Exp. Brain Res 186, 273-282.

Blangero A, Gaveau V, Luaute J, Rode G, Salemme R, Guinard M, Boisson D, Rossetti Y, Pisella L (2008). A hand and a field effect in on-line motor control in unilateral optic ataxia. Cortex, 44, 560-568.

Brown MRG, Vilis T, Everling S (2007). Frontoparietal Activation With Preparation for Antisaccades. J Neurophysiol, 98, 1751-1762.

Butler SH, Gilchrist ID, Ludwig JCH, Muir K, Harvey M (2006). Impairments of oculomotor control in a patient with a right temporo-parietal lesion. Cogn Neuropsychology 23, 990–999

Butler SH, Rossit S, Gilchrist ID, Ludwig CJH, Olk B, Muir K, Reeves I, Harvey M (2009). Non-lateralised deficits in anti-saccade performance in patients with hemispatial neglect. Neuropsychologia, 47, 2488-2495.

Carey DP, Harvey M, Milner AD (1996). Visuomotor sensitivity for shape and orientation in a patient with visual form agnosia. Neuropsychologia, 34, 329-337.

Carey DP, Dijkerman HC, Milner AD (2009). Pointing to two imaginary targets at the same time. Bimanual allocentric and egocentric localization in visual form agnostic D.F. Neuropsychologia 47, 1469-1475.

Carey DP, Dijkerman HC, Murphy KJ, Goodale MA, Milner AD (2006). Pointing to places and spaces in a patient with visual form agnosia. Neuropsychologia, 44, 1584-1594.

Chieffi S, Gentilucci M, Allport A, Sasso E, Rizzolatti G (1993). Study of selective reaching and grasping in a patient with unilateral parietal lesion – dissociated effects of residual spatial neglect. Brain, 116, 1119-1137.

Cohen NR, Cross ES, Tunik E, Grafton ST, Culham JC (2009). Ventral and dorsal stream contributions to the online control of immediate and delayed grasping: a TMS approach. Neuropsychologia 47, 1553–1562.

Colby DL, Duhamel JR (1996). Spatial representations for action in parietal cortex. Cogn Brain Res, 5, 105-115.

Colby CL, Duhamel JR, Goldberg ME (1996). Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. J Neurophysiol 76, 2841–2852.

Collins T, Vergilino-Perez D, Delisle L, Dore-Mazars K (2008). Visual Versus Motor Vector Inversions in the Antisaccade Task: A Behavioral Investigation With Saccadic Adaptation. J Neurophysiol, 99, 2708-2718.

Connolly JD, Goodale MA, Desouza JX, Menon RS, Vilis T (2000). A Comparison of Frontoparietal fMRI Activation During Anti-Saccades and Anti-Pointing. J Neurophysiol, 84, 1645-1655.

Connolly JD, Goodale MA, Menon RS, Munoz DP (2002). Human fMRI evidence for the neural correlates of preparatory set. Nat Neurosci 5, 1345–1352.

Corbetta M, Shulman GL (2002). Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neuroscience, 3, 201–15.

Crawford JR, Howell DC (1998). Comparing an individual's test score against norms derived from small samples. Clin Neuropsychology 12, 482-486.

Curtis CE, D'Esposito M (2006). Selection and maintenance of saccade goals in the human frontal eye Welds. J Neurophysiol 95, 3923–3927.

Curtis CE, Rao VY, D'Esposito M (2004). Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci, 24, 3944–3952.

Damasio AR, Damasio H, Chui HC (1980). Neglect following damage to frontal lobe or basal ganglia. Neuropsychologiy, 18, 123-132.

Darling WG, Rizzo M, Butler AJ (2001). Disordered sensorimotor transformations for reaching following posterior cortical lesions. Neuropsychologia, 39, 237-254.

Desmurget M, Prablanc C, Arzi M, Rossetti Y, Paulignan Y, Urquizar C (1996). Integrated control of hand transport and orientation during prehension movements. Exp. Brain Res, 110, 265-278.

Dijkerman HC, Milner AD, Carey DP (1997). Impaired delayed and antisaccades in a visual form agnosic. Exp Brain Res 117(suppl), S66.

Dijkerman HC, Milner AD, Carey DP (1998). Grasping spatial relationships: failure to demonstrate allocentric visual coding in a patient with visual form agnosia. Conscious Cogn, 7, 424-437.

Duhamel JR, Goldberg ME, Fitzgibbon EJ, Sirigu A, Grafman J (1992). Saccadic dysmetria in a patient with a right frontoparietal lesion. Brain, 115, 1387-1402.

Edgeworth J, Robertson IH, McMillan TM (1998). The Balloons Test: a test for visual inattention. Thames Valley Test Company, Bury St Edmunds UK.

Ettinger U, Ffytche DH, Kumari V, Kathmann N, Reuter B, Zelaya F, Williams SCR (2008). Decomposing the Neural Correlates of Anti-saccade Eye Movements Using Event-Related fMRI. Cerebral Cortex, 18, 1148-1159.

Everling S, Fischer B (1998). The antisaccade: a review of basic research and clinical studies. Neuropsychologia 36, 885–899.

Ford KA, Everling S (2009). Neural Activity in Primate Caudate Nucleus Associated With Pro- and Antisaccades. J Neurophysiol, 102, 2334-2341.

Fukumoto-Motishita M, Matsuura M, Ohkubo T, Ohkubo H, Kanaka N, Matsushima E, Taira M, Kojima T, Matsuda T (2009). Hyperfrontality in patients with schizophrenia during saccade and antisaccade tasks: A study with fMRI. Psychiatry and Clinical neurosciences, 63, 209-217.

Gaveau V, Pelisson D, Blangero A, Urquizar C, Prablanc C, Vighetto A, Pisella L (2008). Saccade control and eye–hand coordination in optic ataxia. Neuropsychologia, 46, 475-486.

Girotti F, Casazza M, Musicco M, Avanzini G (1983). Oculomotor Disorders in cortical Lesions in Man: The Role of Unilateral Neglect. Neuropsychologia, 21, 543-553.

Gnadt JW, Anderson RA (1988). Memory related motor planning activity in posterior parietal cortex of macaque. Exp Brain Res 70, 216–220.

Goldberg ME, Bisley J, Powell KD, Gottlieb J, Kusunoki M (2002). The role of the lateral intraparietal area of the monkey in the generation of saccades and visuospatial attention. Ann NY Acad Sci 956, 205-215.

Goldstein JM, Goodman JM, Seidman LJ, Kennedy DN, Makris N, Lee H, Tourville J, Caviness VS, Faraone SV, Tsuang MT (1999). Cortical abnormalities in schizophrenia identified by structual magnetic resonance imaging. Archives of General Psychiatry, 56, 537-547.

Goodale MA, Humphrey GK (1998). The objects of action and perception. Cognition, 67, 181-207.

Goodale MA, Jakobson LS, Keillor JM (1994). Differences in the visual control of pantomimed and natural grasping movements. Neuropsychologia 32, 1159-1178.

Goodale MA, Jakobson, LS, Milner AD, Perrett DI, Benson PJ, Hietanen JK (1994b). The nature and limits of orientation and pattern processing supporting visuomotor control in a visual form agnosic. Journal of Cognitive Neuroscience 6, 46-56.

Goodale MA, Meenan JP, Bülthoff HH, Nicolle DA, Murphy KJ, Racicot CI (1994a). Separate neural pathways for the visual analysis of object shape in perception and prehension. Curr Biol. 4, 604-10.

Goodale MA, Milner AD, Jakobson LS, Carey DP (1991). A neurological dissociation between perceiving objects and grasping them. Nature, 349, 154-156.

Goodale MA, Milner AD (1992). Separate visual pathways for perception and action. Trends in Neurosci 15, 20–25.

Goodale MA, Milner AD (2004). Sight unseen: An exploration of conscieus and unconscious vision. Oxford: Oxford University Press.

Goodale MA, Pelisson D, Prablanc C (1986). Large adjustments in visually guided reaching do not depend on vision of the hand of perception of target displacement. Nature, 320, 748-750.

Goodale MA, Westwood DA, Milner AD (2004). Two distinct modes of control for object-directed action. Prog Brain Res., 144, 131-44.

Graveleau P, Viader F, Cambier J (1986). Subcortical neglect. The Italian Journal of Neurological Sciences, 7, 573-580.

Grea H, Pisella L, Rossetti Y, Desmurget M, Tilikete C, Grafton S, Parablanc C, Vighetto A (2002). A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. Neuropsychologia, 40, 2471-2480.

Grefkes C, Fink GR (2005). The functional organization of the intraparietal sulcus in humans and monkeys. J Anat 207, 3–17.

Guitton D, Buchtel HA, Douglas RM (1985). Frontal-lobe lesions in man cause difficulties in supressing reflexive glances and generating goal-directed saccades. Exp Brain Res, 58, 455-472.

Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, Bilker WB, Gur RC (2000). Reduced dorsal and orbita prefrontal gray matter volumes in schizophrenia. Archives of General Psychiatry, 57, 761-768.

Hallett PE (1978). Primary and secondary saccades to goals defined by instructions. Vision Research, 18, 1279-1296.

Halligan PW, Manning L, Marshall JC (1990). Individual variation in line bisection: a study of four patients with right hemisphere damage and normal controls. Neuropsychologia, 28, 1043-1051.

Halligan PW, Fink GR, Marshall JC, Vallar G (2003). Spatial cognition: evidence from visual neglect. Trends Cogn Sci, 7, 125-133.

Hanes DP, Patterson WF, Schall JD (1998). Role of Frontal Eye Fields in Countermanding Saccades: Visual, Movement, and Fixation Activity. J Neurophysiol, 79, 817-834.

Harvey M, Olk B, Muir K, Gilchrist ID (2002). Manual responses and saccades in chronic and recovered hemispatial neglect: a study using visual search. Neuropsychologia, 40, 705-717.

Harvey M, Gilchrist ID, Olk B, Muir K (2003). Eye-movement patterns do not mediate size distortion effects in hemispatial neglect: looking without seeing. Neuropsychologia, 41, 1114-1121.

Harvey M, Milner AD, Roberts RC (1995). An Investigation of Hemispatial Neglect Using the Landmark Task. Brain and Cognition, 27, 59-78.

Heilman KM, Bowers D, Valenstein E, Watson RT (1993). Disorders of visual attention. Baillieres Clin Neurol, 2, 389-413.

Heilman KM, Valenstein E (1972). Frontal lobe neglect in man. Neurology, 22, 660-664.

Heilman KM, Valenstein E, Watson RT (1985). The neglect syndrom. In Fredericks JAM (ed) Handbook of Clinical Neurology, Vol 1 (45) Clinical Neuropsychology, elsevier science publishers bv (the netherlands).

Hikosaka O, Takikawa Y, Kawagoe R (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. Physiological Reviews, 80, 953-978.

Himmelbach M, Karnath HO (2003). Goal-directed hand movements are not affected by the biased space representation in spatial neglect. J Cogn Neurosci., 15, 972-80.

Himmelbach M, Karnath HO (2005). Dorsal and ventral stream interaction: Contributions from optic ataxia. Journal of Cognitive Neuroscience, 17, 632-640.

Himmelbach M, Nau M, Zündorf I, Erb M, Perenin MT, Karnath HO (2009). Brain activation during immediate and delayed reaching in optic ataxia. Neuropsychologia 47, 1508–1517.

Humphrey K, Goodale MA, Jakobson LS, Servos P (1994). The role of surface information in object recognition: studies of a visual form agnostic and normal subjects. Perception 23, 1457–1481.

Hussain M, Kennard C (1996). Visual neglect associated with frontal lobe infarction. Journal of Neurology, 243, 652-657.

Husain M, Mannan S, Hodgson T, Wojciulik E, Driver J, Kennard C (2001). Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. Brain, 121, 941–952.

Husain M, Shapiro K, Marin J, Kennard C (1997). Abnormal temporal dynamics of visual attention in spatial neglect patients. Nature, 385, 154-156.

James WT, Culham J, Humphrey GK, Milner AD, Goodale MA (2003). Ventral occipital lesion impair object recognition but not object directed grasping: an fMRI study. Brain 126, 2463–2475.

Johnston K, Everling S (2006). Monkey Dorsolateral Prefrontal Cortex Sends Task-Selective Signals Directly to the Superior Colliculus. Journal of neuroscience, 26, 12471-12478.

Karnath HO, Berger MF, Kuker W, Rorden C (2004). The anatomy of spatial neglect based on voxelvise statistical analysis: a study of 140 patients. Cereb Cortex, 14,1164–1172.

Karnath HO, Dick H, Konczak J (1997). Kinematics of goal-directed arm movements in neglect: control of hand in space. Neuropsychologia, 35, 435-444.

Karnath HO, Ferber S, Himmelbach M (2001). Spatial awareness is a function of the temporal noth the posterior parietal lobe. Nature, 411, 950-953.

Karnath HO, Perenin MT (2005). Cortical control of visually guided reaching: Evidence from patients with optic ataxia. Cerebral cortex, 15, 1561-1569.

Komilis E, Pelisson D, Prablanc C (1993). Error processing in pointing at randomly feedback-induced double-step stimuli. J. Motor Behav., 25, 299–308.

Konczak J, Himmelbach M, Perenin MT, Karnath HO (1999). Do patients with neglect show abnormal hand velocity profiles during tactile exploration of peripersonal space? Exp. Brain Res., 128, 219-223.

Konczak J, Karnath HO (1998). Kinematics of goal-directed arm movements in neglect: control of hand velocity. Brain Cogn., 37, 387-403.

Kunimatsu J, Tanaka M (2010). Roles of the Primate Motor Thalamus in the Generation of Antisaccades. Journal of Neuroscience, 30, 5108-5117.

Lawrence NS, Ross TJ, Hoffmann R, Garavan H, Stein EA (2003). Multiple neuronal networks mediate sustained attention. J Cogn Neuroscience, 15, 1028–38.

Leber AB, Turk-Browne NB, Chun MM (2008). Neural predictors of moment-to-moment fluctuations in cognitive flexibility. Proceedings of the National Academy of Sciences of the United States of America, 105, 13592-13597.

Lee H, Abegg M, Rodriguez A, Koehn J, Barton JJS (2010). Why do humans make antisaccade errors? Exp Brain Res, 201, 65-73.

Levy I, Schluppeck D, Heeger DJ, Glimcher PW (2007). Specificity of human cortical areas for reaches and saccades. J Neurosci 27, 4687-4696.

Liu CL, Chiau HY, Tseng P, Hung DL, Tzeng OJL, Muggleton NG, Juan CH (2010). Antisaccade Cost Is Modulated by Contextual Experience of Location Probability. J Neurophysiol, 103, 1438-1447.

Luks TL, Sun FT, Dale CL, Miller WL, Simpson GV (2008). Transient and sustained brain activity during anticipatory visuospatial attention. Neuroreport, 19, 155-159.

Machado L, Rafal RD (2004). Control of fixation and saccades during an anti-saccade task: an investigation in humans with chronic lesions of oculomotor cortex. Exp Brain Res, 156, 55-63.

Malhotra P, Coulthard E, Husain M (2009). Role of right posterior parietal cortex in maintaining attention to spatial locations over time.Brain, 132, 645–660.

Malhotra P, Jaeger HR, Parton A, Greenwood R, Playford ED, Brown MM, Driver J, Husain M (2005). Spatial working memory capacity in unilateral neglect. Brain, 128, 424-435.

Massen C (2004). Parallel programming of exogenous and endogenous components in the antisaccade task. Quarterly Journal of Experimental Psychology Section A - Human experimental Psychology, 57, 475-498.

McIntosh R D, Dijkerman HC, Mon-Williams M, Milner AD (2004). Grasping what is graspable: Evidence from visual form agnosia. Cortex, 40, 695-702.

McIntosh RD, Pritchard CL, Dijkerman HC, Milner AD, Roberts RC (2001). Prehension and perception of size in left visual neglect. Behavioural Neurology, 13, 3-15.

McIntosh RD, Rossit S, Malhotra P, Butler SH, Harvey M (2010). The automatic pilot of the hand is unbalanced by visual neglect. Behavioural Neurology, 23, 249-251.

Medendorp WP, Goltz HC, Vilis T (2005). Remapping the Remembered Target Location for Anti-Saccades in Human Posterior Parietal Cortex. J Neurophysiol, 94, 734-740.

Meyniel C, Rivaud-Pechoux S, Damier P, Gaymard B (2005). Saccade impairments in patients with fronto-temporal dementia. J Neurol Neurosurg Psychiatry, 76, 1581-1584.

Milner AD, Dijkerman HC, Carey DP (1999). Visuospatial processing in a pure case of visual from agnosia. In: Burgess N, Jeffrey KJ, O'Keefe J (eds). The hippocampal and parietal functions of spatial cognition. Oxford University Press, Oxford, pp 443–466.

Milner AD, Dijkerman HC, McIntosh RD, Rossetti Y, Pisella L (2003). Delayed reaching and grasping in patients with optic ataxia. Progress in Brain Research, 142, 225-242.

Milner AD, Dijkerman HC, Pisella L, McIntosh RD, Tilikete C, Vigetto A, Rossetti Y (2001). Grasping the past: delay can improve visuomotor performance. Curr Biol 11, 1896–1901.

Milner AD, Goodale MA (1995). The visual brain in action. Oxford University Press, Oxford.

Milner AD, Goodale MA (2006). The visual brain in action, 2nd edn., Oxford University Press, Oxford.

Milner AD, Goodale MA (2008). Two visual systems re-viewed. Neuropsychologia 46,774–785.

Milner AD, Harvey M (1995). Distortion of size perception in visuospatial neglect. Current Biology, 5, 85-89.

Milner AD, Harvey M (2006). Visuomotor control of spatially directed action. Imagery and spatial cognition: methods, models and clinical assessment. Advances in Consciousness Research, 66, 297-322.

Milner AD, Harvey M, Pritchard CL (1998). Visual size processing in spatial neglect. Experimental Brain Research, 123, 192-200.

Milner AD, Paulignan Y, Dijkerman HC, Michel F, Jeannerod M (1999b). A paradoxical improvement of misreaching in optic ataxia: new evidence for two separate neural systems for visual localization. Proc Biol Sci-B 266, 2225–2229.

Milner AD, Perrett DI, Johnston RS, Benson PJ, Jordan TR, Heeley DW, Bettucci D, Mortana F, Mutani R, Terazzi E, Davidson DLW (1991). Perception and action in 'visual form agnosia'. Brain 114, 405–428.

Mokler A, Fischer B (1999). The recognition and correction of in voluntary prosaccades in an antisaccade task. Exp Brain Res, 125, 511-516.

Mort JD, Malhotra P, Mannan SK, Rorden C, Pambakian A, Kennard C, Husain M (2003). The anatomy of visual neglect. Brain 126, 1986–1997.

Munoz DP, Everling S (2004). Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 5, 218-228.

Munoz DP, Istvan PJ (1998). Lateral inhibitory interactions in the intermediate layers of the monkey superior colliculus. Journal of Neurophysiology, 79, 1193-1209.

Munoz DP, Wurtz RH (1993). Fixation Cells in Monkey Superior Colliculus I. Characteristics of Cell Discharge. Journal of Neurophysiology, 70, 559-575.

Müri RM, Vermersch AL, Rivaud S, Gaymard B, Pierrot Deseilligny C (1996). Effects of single-Pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortices during memory-guided saccades in humans. Journal of Neurophysiology, 76, 2102-2106.

Müri RM, Cazzoli D, Nyffeler T, Pflugshaupt T (2009). Visual exploration pattern in hemineglect. Psychological Research, 73, 147-57.

Murphy KJ, Racicot CI & Goodale MA (1996). The use of visuomotor cues as a strategy for making perceptual judgments in a patient with visual form agnosia. Neuropsychology, 10, 396-401.

Na DL, Adair JC, Kang Y, Chung CS, Lee KH, Heilman KM (1999). Motor perseverative behavior on a line cancellation task. Neurology, 52, 1569-1576.

Nichelli P, Rinaldi M, Cubelli R (1989). Selective spatial attention and length representation in normal subjects and in patients with unilateral spatial neglect. Brain and Cognition, 9, 57-70.

Niemeier M, Karnath HO (2003). Stimulus-Driven and Voluntary Saccades Are Coded in Different Coordinate Systems. Current Biology, 13, 585-589.

Nyffeler T, Egli A, Pflugshaupt T, von Wartburg R, Wurtz P, Mosimann U, Hess CW, Müri RM (2005). The role of the human posterior parietal cortex in memory-guided saccade execution: a doublepulse transcranial magnetic stimulation study. Eur J Neurosci 22, 535-538.

Nyffeler T, Müri RM, Bucher-Ottiger Y, Pierrot-Deseilligny C, Gaymard B, Rivaud-Pechoyx S (2007). Inhibitory control of the human dorsolateral prefrontal cortex during the anti-saccade paradigm - a transcranial magnetic stimulation study. European Journal of Neuroschience, 26, 1381-1385.

Olk B, Chang E, Kingstone A, Ro T (2006). Modulation of antisaccades by transcranial magnetic stimulation of the human frontal eye field. Cerebral Cortex, 16, 76-82.

Olk B, Harvey M, Gilchrist ID (2002). First saccades reveal biases in recovered neglect. Neurocase, 8, 306-313.

Olk B, Kingstone A (2003). Why are antisaccades slower than prosaccades? A novel finding using a new paradigm. Neuroreport, 14, 151–155.

Olk B, Kingstone A (2009). A new look at aging and performance in the antisaccade task: The impact of response selection. European Journal of Cognitive Psychology, 21, 406-427.

Olson CR, Gettner SN (2002). Neuronal activity related to rule and conflict in macaque supplementray eye field. Physiology & Behaviour, 77, 663-670.

Pelisson D, Prablanc C, Goodale MA, Jeannerod M (1986). Visual control of reaching movements without vision of the limb. II. Evidence of fast unconscious processes correcting the trajectory of the hand to the final position of a double-step stimulus. Exp. Brain Res., 62, 303-311.

Petit L, Dubois S, Tzourio N, Dejardin S, Crivello F, Michel C, Etard O, Denise P, Roucoux A, Mazoyer B (1999). PET Study of the Human Foveal Fixation System. Human Brain Mapping, 8, 28-43.

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y (1991). Cortical control of memory-guided saccades in man. Exp Brain Res, 83, 607-617.

Pisella L, Berberovic N, Mattingley JB (2004). Impaired working memory for location but not for coulour of spahe in visual neglect: a comparison of parietal and non-parietal lesions. Cortex, 40, 379-390.

Pisella L, Grea H, Tilikete C, Vighetto A, Desmurget M, Rode G, Boisson D, Rossetti Y (2000). An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. Nature Neuroscience, 3, 729-736.

Ploner CJ, Gaymard BM, Rivaud-Pechoux S, Pierrot-Deseilligny C (2005). The Prefrontal Substrate of Reflexive Saccade Inhibition in Humans. Biol Psychiatry, 57, 1159-1165.

Posner MI, Walker JA, Friedrich FJ, Rafal RD (1984). Effects of parietal injury on covert orienting of attention. J Neurosci, 4, 1863-1874.

Pritchard CL, Milner AD, Dijkerman HC, MacWalter RS (1997). Visuospatial neglect: veridical coding of size for grasping but not for perception. Neurocase, 3, 437–443.

Rastelli F, Funes MJ, Lupianez J, Duret C, Bartolomeo P (2008). Left visual neglect: Is the disengage dieficit space- or object-based? Exp Brain Res, 187, 439-446.

Reuter B, Jaeger M, Bottlender R, Kathmann N (2007). Impaired action control in schizophrenia: The role of volitional saccade initiation. Neuropsychologia, 45, 1840-1848.

Rogers G, Smith D, Schenk T (2009). Immediate and delayed actions share a common visuomotor transformation mechanism: A prism adaptation study. Neuropsychologia, 47, 1546-1552.

Rossit R, Harvey M (2008). Age-related differences in corrected and inhibited pointing movements. Experimental Brain Research, 185, 1-10.

Rossit S, Malhotra P, Muir K, Duncan G, Reeves I, Birschel P, Harvey M (2009a). The neural basis of visuomotor deficits in hemispatial neglect. Neuropsychologia, 47, 2149–2153.

Rossit S, Malhotra P, Muir K, Reeves I, Duncan G, Livingstone K, Jackson H, Hogg C, Castle P, Learmonth G, Harvey M (2009c). No neglect- specific deficits in reaching tasks. Cerebral Cortex, 19, 2616-2624.

Rossit S, Malhotra P, Muir K, Duncan G, Reeves I, Duncan G, Harvey M (2011). The role of right temporal lobe structures in off-line action: evidence from lesion-behavior mapping in stroke patients. Cerebral Cortex, 21, 2751-2761.

Rossit S, Muir K, Reeves I, Duncan G, Livingstone K, Jackson H, Castle P, Harvey M (2008). Non-lateralized impairments in anti- but not pro-pointing in patients with hemispatial neglect. Journal of Vision, 8, 50.

Rossit S, Muir K, Reeves I, Duncan G, Birschel P, Harvey M (2009b). Immediate and delayed reaching in hemispatial neglect. Neuropsychologia 47, 1563-1572.

Rossit S, Szymanek L, Butler SH, Harvey M (2010). Memory-guided saccade processing in visual form agnosia (patient DF). Exp Brain Res 200 (1), 109-116.

Schlag-Rey M, Amador N, Sanchez H, Schlag J (1997). Antisaccade performance predicted by neuronal activity in the supplementary eye field. Nature, 390, 398-401.

Schluppeck D, Curtis CE, Glimcher PW, Heeger DJ (2006). Sustained activity in topographic areas of human posterior parietal cortex during memory-guided saccades. J Neurosci 26, 5098–5108.

Schluppeck D, Glimcher P, Heeger DJ (2006). Topographic organization for delayed saccades in human posterior parietal cortex. J Neurophysiol 94, 1372–1384.

Singhal A, Kaufman L, Valyear K, Culham J (2006). fMRI reactivation of the human lateral occipital complex during delayed actions to remembered targets. Visual cognition, 14, 125-128.

Singh-Curry V, Husain M (2009). The functional role of the inferior paretal lobe in the dorsal and ventral stream dichotomy. Neuropsychologia, 47, 1434-1448.

Smyrnis N, Evdokimidis I, Stefanis NC, Constantinidis TS, Avramopoulos D, Theleritis C, Paximadis C, Efstratiadis C, Kastrinakis G, Stefanis CN (2002). The antisaccade task in a sample of 2,006 young males II. Effects of task parameters. Exp Brain Res, 147, 53-63.

Stone SP, Patel P, Greenwood RJ, Halligan PW (1992). Measuring visual neglect in acute stroke and predicting ist recovery: the visual neglect recovery index. J Neurol Neurosurg Psychiatry, 55, 431-436.

Sturm W, de Simone A, Krause BJ, Specht K, Hesselmann V, Radermacher I, Herzog H, Tellmann L, Müller-Gärtner HW, Willmes K (1999). Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. Neuropsychologia, 37, 797-805.

Taylor AJG, Hutton SB (2009). The effects of task instructions on pro and antisaccade performance. Exp Brain Res, 195, 5-14.

Ungeleider LG, Mishkin M (1982). Two Cortical Visual Systems. In: Analysis of Visual Behavior. Edited by Ingle DJ, Goodale MA, Mansfield RJW, Cambridge, MA, MIT Press, 549-586.

Vallar G, Perani D (1986). The Anatomy of unilateral neglect after right-hemisphere stroke lesions - a clinical CT-scan correlation study in man. Neuropsychologia, 24, 609-622.

Van Der Werf J, Jensen O, Fries P, Medendorp WP (2008). Gamma-Band Activity in Human Posterior Parietal Cortex Encodes the Motor Goal during Delayed Prosaccades and Antisaccades. Journal of Neuroscience, 28, 8397-8405.

Vandenberghe R, Gitelman DR, Parrish TB, Mesulam MM (2001). Functional specificity of superior parietal mediation of spatial shifting. Neuroimage, 14, 661–73.

Walker R, Findlay JM (1996). Saccadic eye movement programming in unilateral neglect. Neuropsychologia 34, 493-508.

Watson RT, Heilman KM (1979). Thamalic neglect. Neurology, 29, 690-694.

Watson RT, Heilman KM, Cauthen JC, King FA (1973). Neglect after cingulectomy, Neurology, 23, 1003-1007.

Wegener SP, Johnston K, Everling S (2008). Microstimulation of monkey dorsolateral prefrontal cortex impairs antisaccade performance. Exp Brain Res, 190, 463-473.

Welch K, Stuteville P (1958). Experimental Production of Unilateral Neglect in Monkeys. Brain, 81, 341-347.

Westwood DA, Goodale MA (2003). Perceptual illusion and the realtime control of action. Spat Vis 16, 243–254.

Wilson BA, Alderman N, Burgess PW, Emslie H, Evans JJ (1996). Behavioural Assessment of the Dysexecutive Syndrom (BADS). Thames Valley Test Company.

Wilson BA, Cockburn J, Halligan P (1987). Behavioural Inattention Test. Titchfield, Thames Valley Test Company.

Wise SP, Murray EA, Gerfen CR (1996). The frontal cortex basal ganglia system in primates. Critical Reviews in Neurobiology, 10, 317-356.